# Diabetes care: Where are we headed?

John B. Buse, MD, PhD
jbuse@med.unc.edu

UNC SCHOOL OF MEDICINE

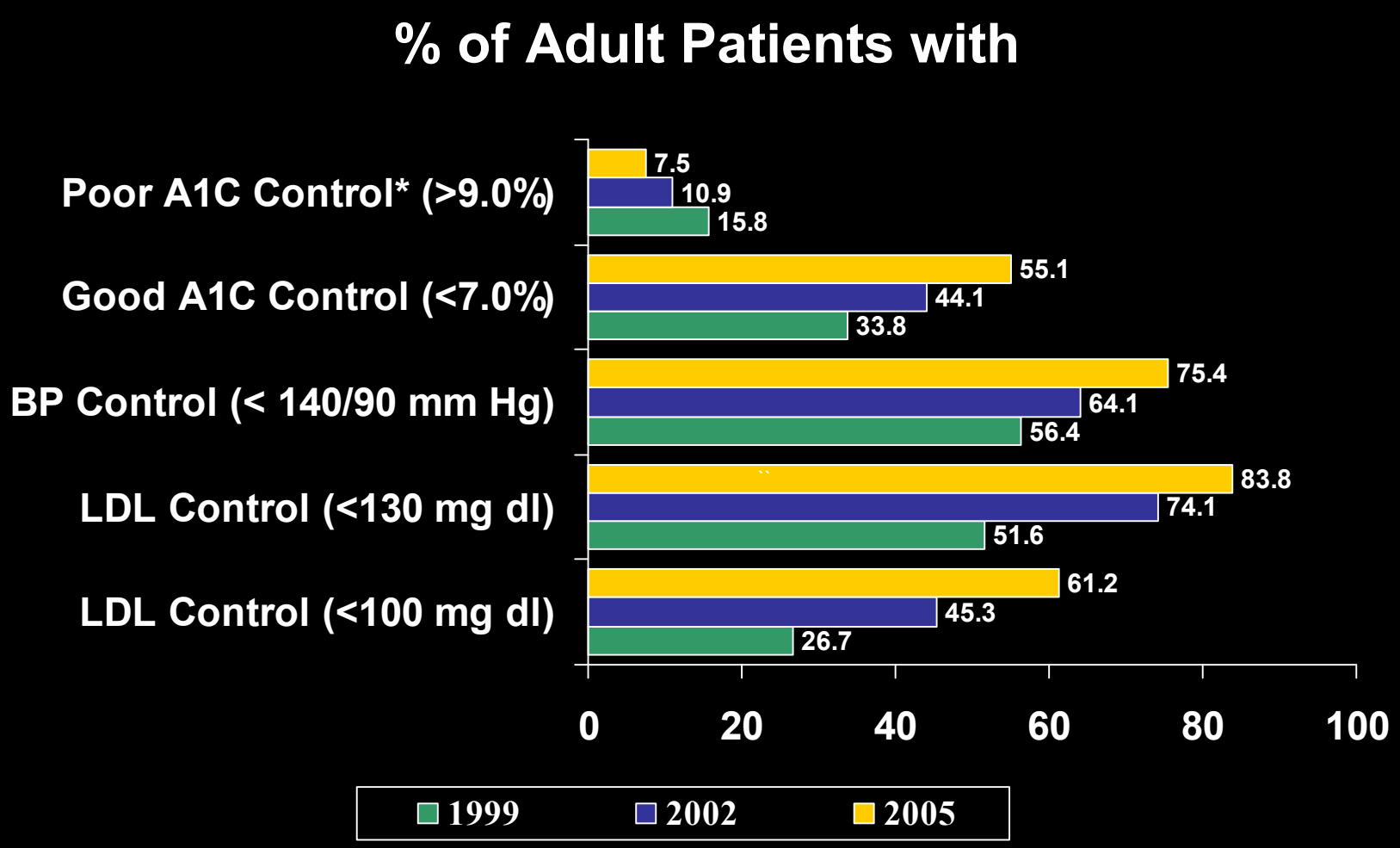
# Diabetes Impact

**24 million with diabetes, perhaps 70 million with "prediabetes"**

| | Daily | Annually |
|---|---|---|
| Cost | $476,712,329 | $174,000,000,000 |
| New cases | 4,658 | 1,700,000 |
| Deaths | 641 | 234,000 |
| Amputations | 195 | 71,000 |
| ESRD | 129 | 47,000 |
| Blindness | 66 | 24,000 |

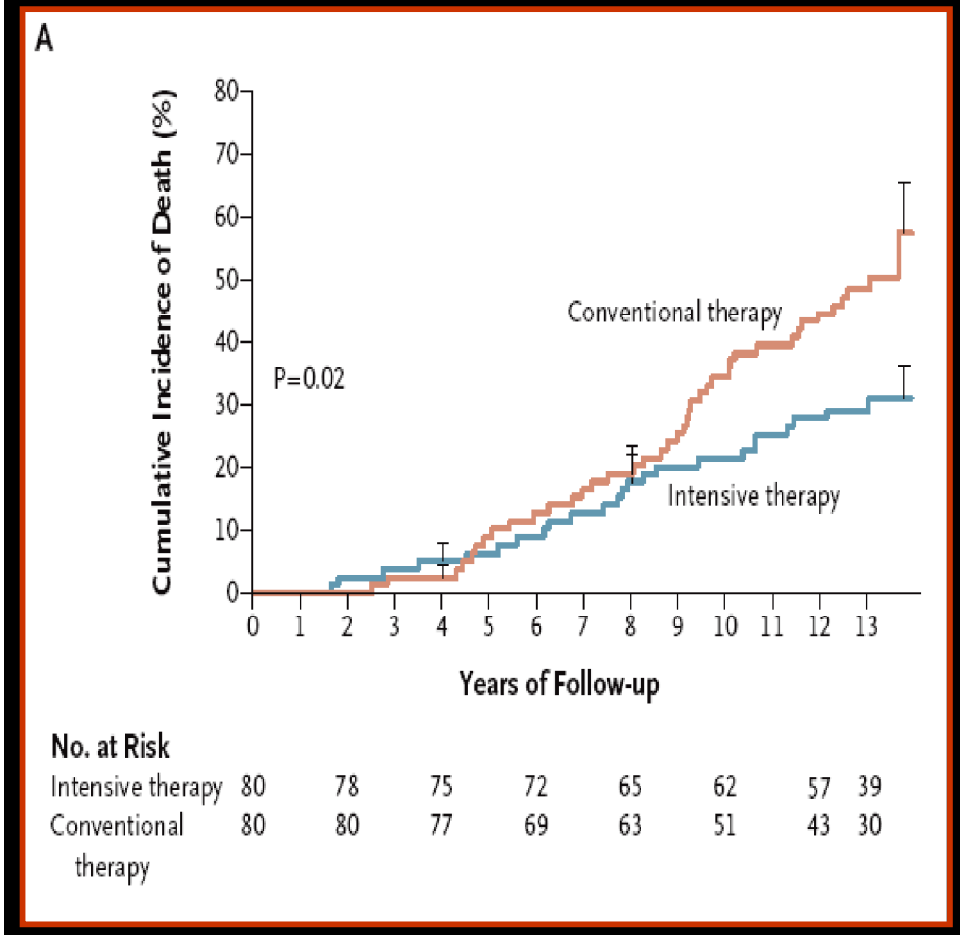
**Centers for Disease Control and Prevention. National diabetes fact sheet: general information and national estimates on diabetes in the United States, 2007. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, 2008.**

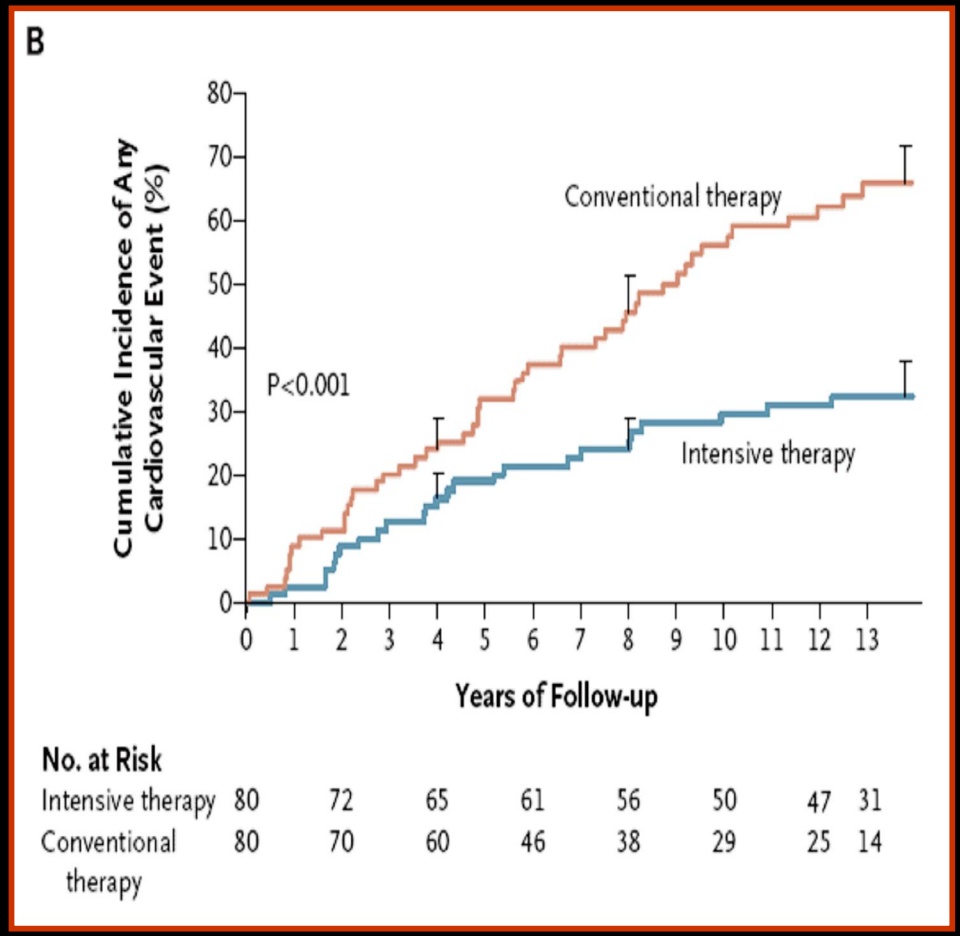
# Improvement In Key Clinical Measures




* Lower is better for this measure.

# STENO -2
# Multi-Risk Factor Intervention in Type 2 DM

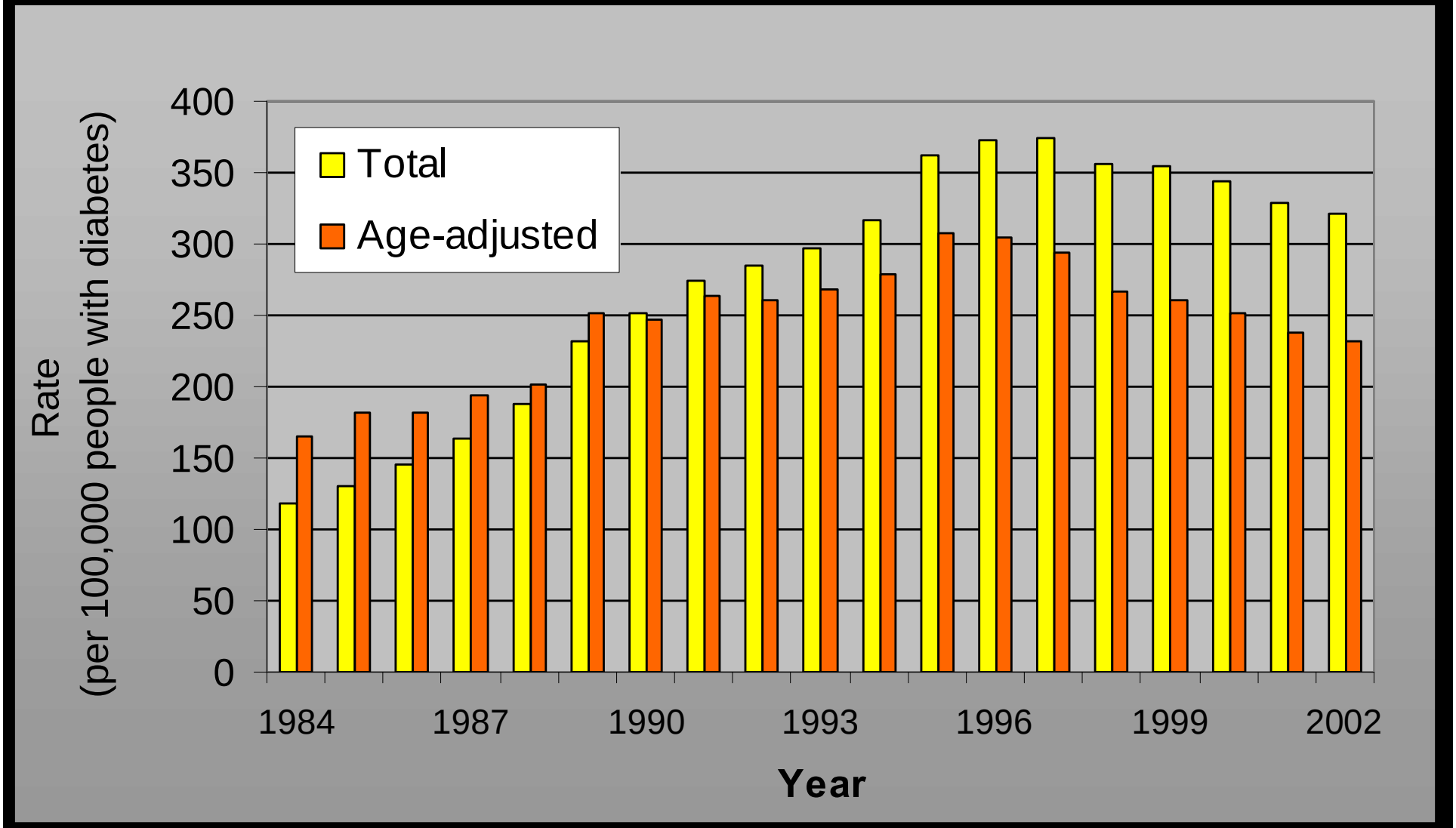



**Intensive group end results: A1C 7.7%, BP 140/74, LDL 71 mg/dL, HDL 51 mg/dl, TG 99 mg/dL, aspirin 85%**

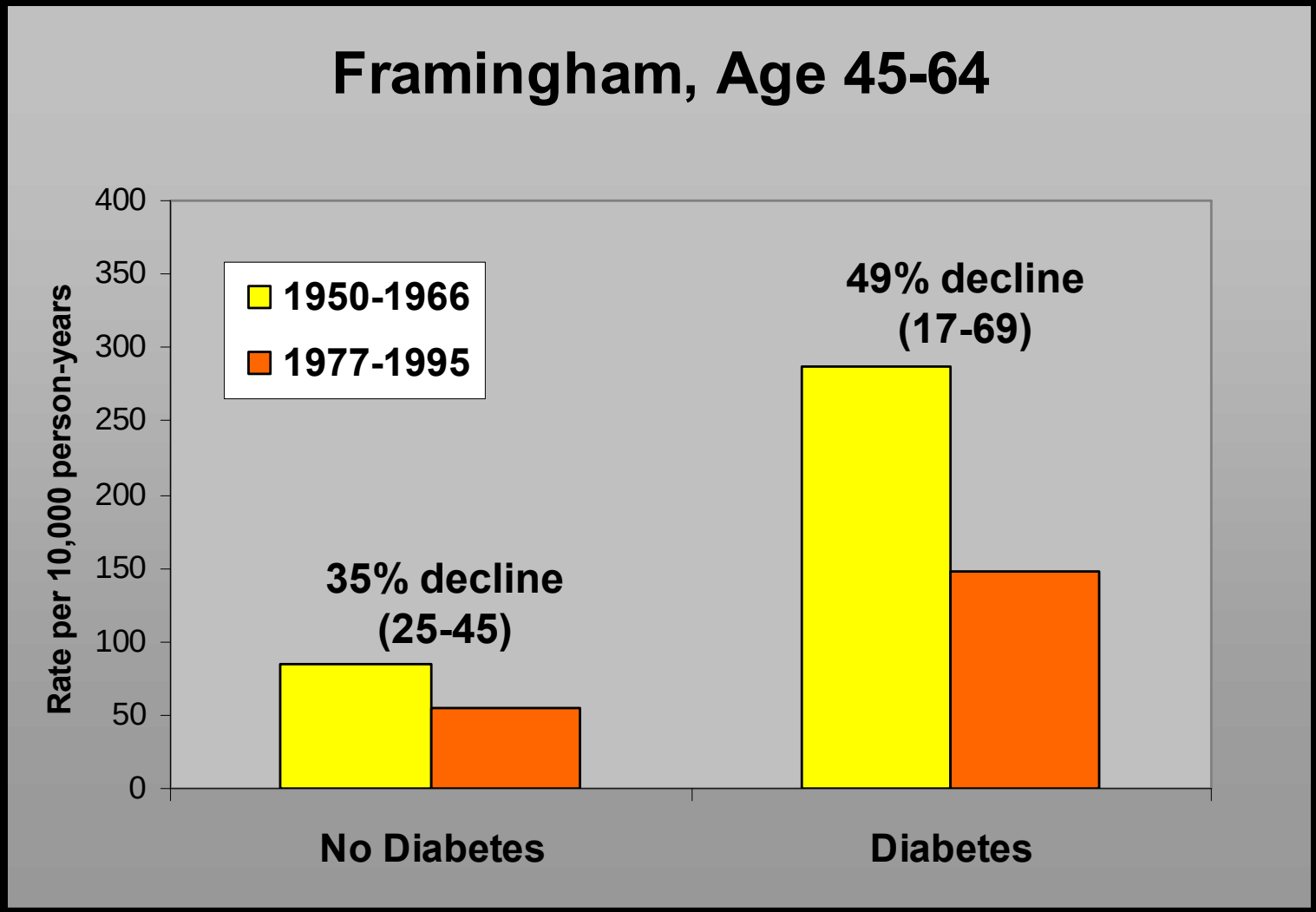
**Gaede P. *N Engl J Med* 2008; 358: 580-591**

# Incidence of ESRD




Data from Centers for Disease Control and Prevention, Division of Diabetes Translation; available at http://www.cdc.gov/diabetes/statistics/esrd/fig7.htm

# Incidence of Cardiovascular Disease




Fox CS, et al. *JAMA.* 2004;292:2495-2499

# An Optimist's View: Summary and Conclusions

- Glycemic control is improving and generally good
- With systematic care, cardiovascular risk factor control is likewise generally good
- Simultaneous control of glycemia, blood pressure, lipids, smoking and platelet hyperaggregability is associated with improvements in outcomes
- The natural history of prediabetes and diabetes in the 21st century is uncertain, but the prognosis appears excellent with medical management

- Should we go further in managing diabetes using classical techniques?

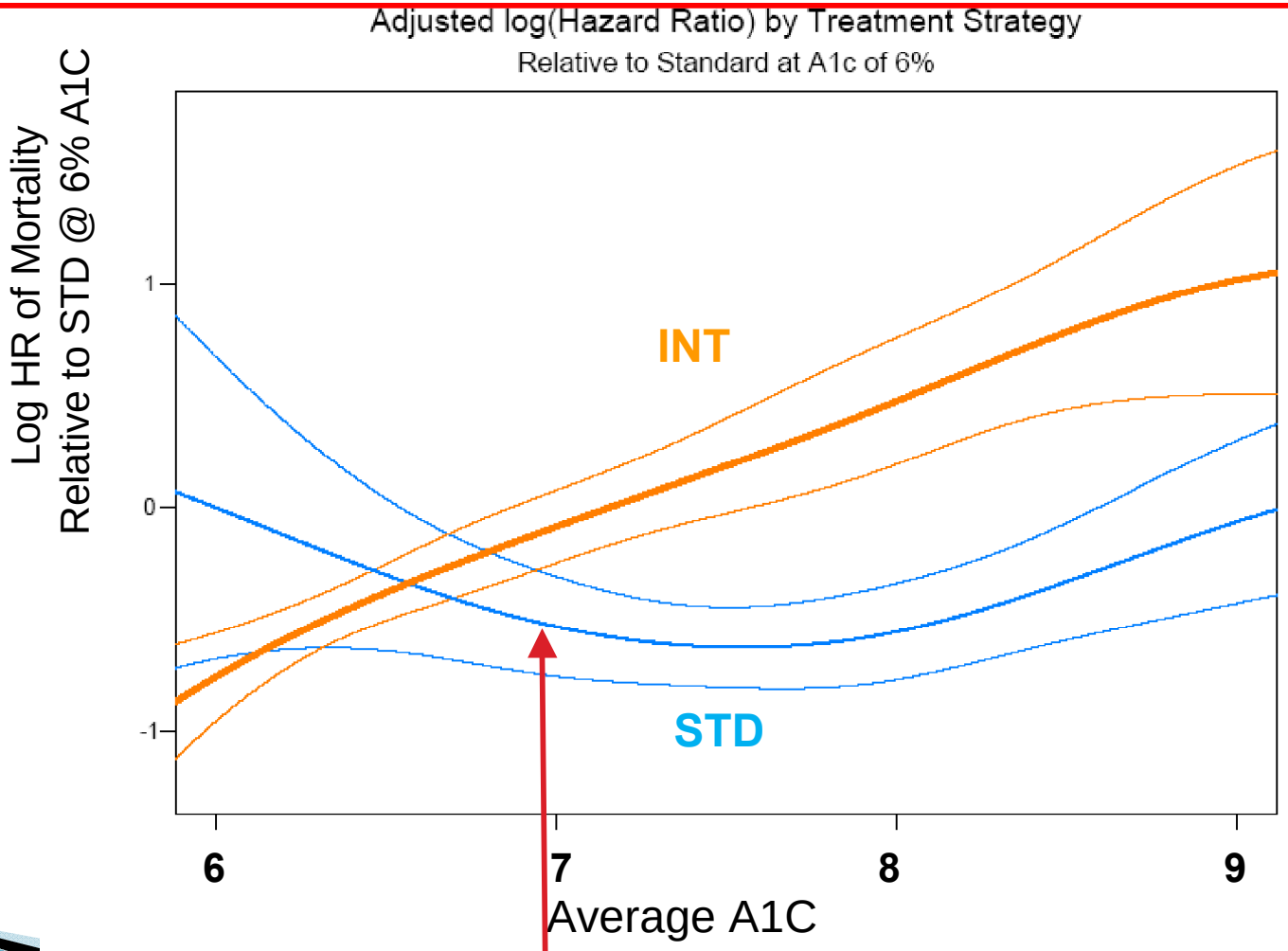
# Summary: Glucose Lowering on CVD in Type 2 Diabetes

| | ACCORD | VADT | ADVANCE |
|---|---|---|---|
| Primary outcome | Non-fatal MI<br>Non-fatal stroke<br>CVD death | Non-fatal MI<br>Non-fatal stroke<br>CVD death<br>CHF Hospitalization<br>Revascularization | Non-fatal MI<br>Non-fatal stroke<br>CVD death |
| Hazard Ratio for primary outcome (95% CI) | 0.90<br>(0.78 – 1.04) | 0.87<br>(0.73 – 1.04) | 0.94<br>(0.84 – 1.06) |
| Hazard Ratio for mortality (95% CI) | 1.22<br>(1.01 – 1.46)* | 1.07<br>(0.80 – 1.42) | 0.93<br>(0.83 – 1.06) |

*$P$=0.04

# ACCORD:
# Risk of Death over Range of Average A1C

**Steady increase of risk from 6% to 9% A1C in INT strategy**



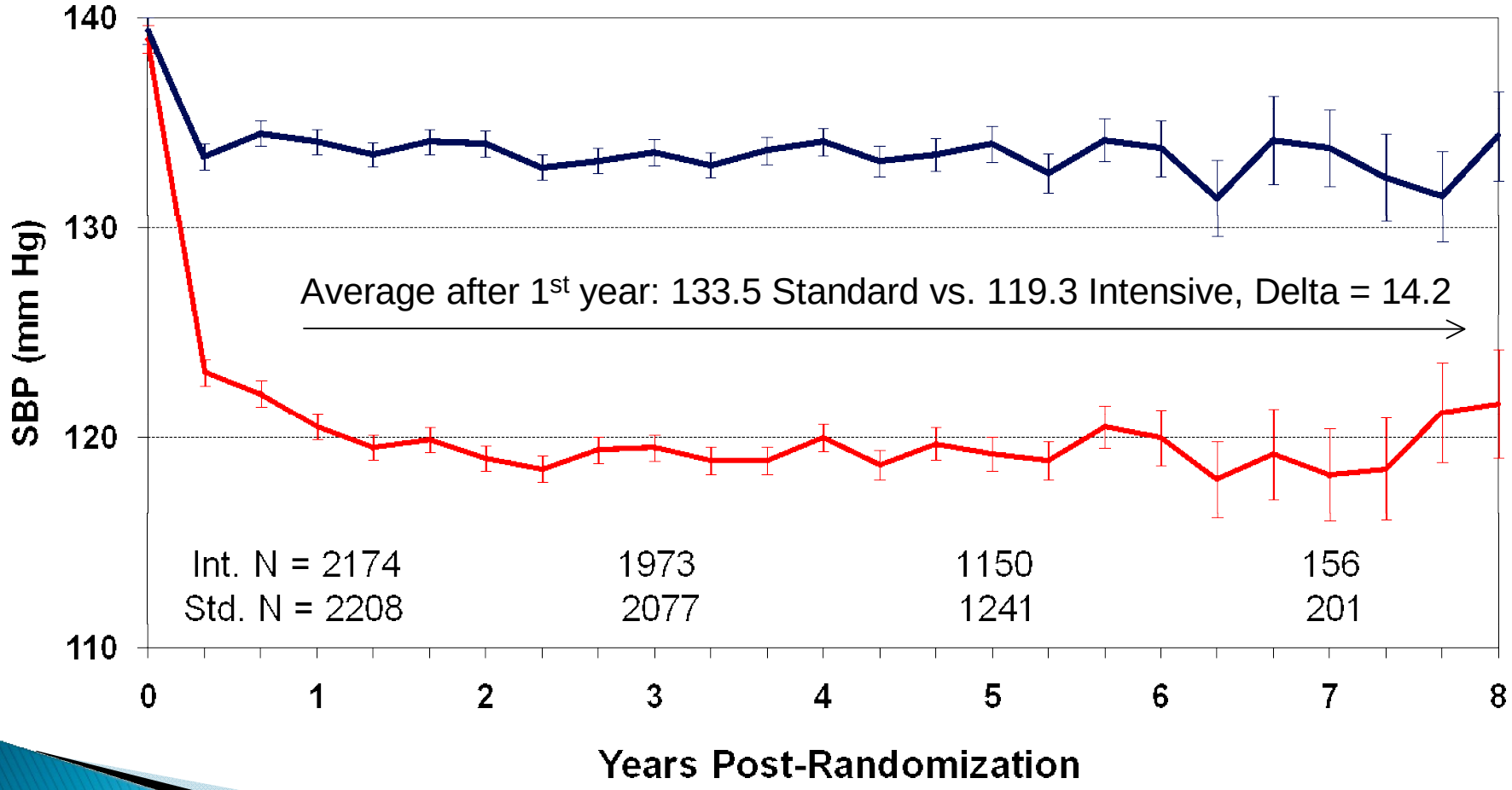

**Excess risk with INT vs STD above A1C 7%**

Action to Control Cardiovascular Risk in D
ACCORD

# Systolic Pressures (mean ± 95% CI)

Mean # Meds

| | | | | |
|---|---|---|---|---|
| Intensive: | 3.2 | 3.4 | 3.5 | 3.4 |
| Standard: | 1.9 | 2.1 | 2.2 | 2.3 |




Action to Control Cardiovascular Risk in Diabetes
ACCORD

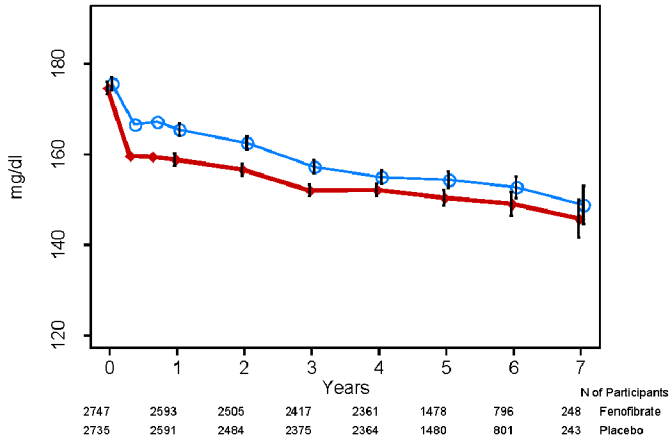
# Primary & Secondary Outcomes

| | Intensive Events (%/yr) | Standard Events (%/yr) | HR (95% CI) | P |
|---|---|---|---|---|
| Primary | 208 (1.87) | 237 (2.09) | 0.88 (0.73-1.06) | 0.20 |
| Total Mortality | 150 (1.28) | 144 (1.19) | 1.07 (0.85-1.35) | 0.55 |
| Cardiovascular Deaths | 60 (0.52) | 58 (0.49) | 1.06 (0.74-1.52) | 0.74 |
| Nonfatal MI | 126 (1.13) | 146 (1.28) | 0.87 (0.68-1.10) | 0.25 |
| Nonfatal Stroke | 34 (0.30) | 55 (0.47) | 0.63 (0.41-0.96) | 0.03 |
| Total Stroke | 36 (0.32) | 62 (0.53) | 0.59 (0.39-0.89) | 0.01 |

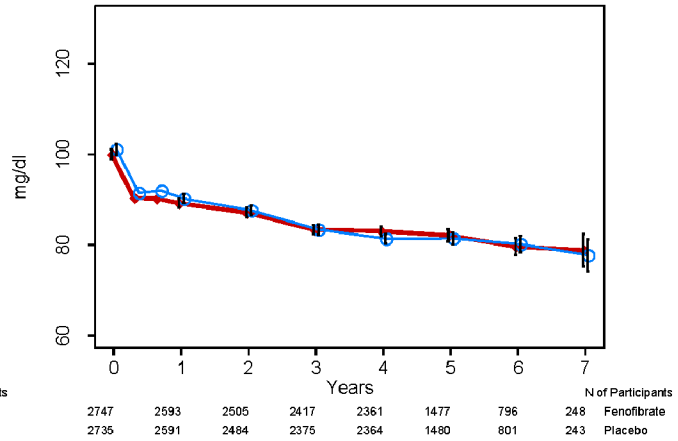
*Also examined Fatal/Nonfatal HF (HR=0.94, p=0.67), a composite of fatal coronary events, nonfatal MI and unstable angina (HR=0.94, p=0.50) and a composite of the primary outcome, revascularization and unstable angina (HR=0.95, p=0.40)*

# Plasma Lipid Levels During Trial

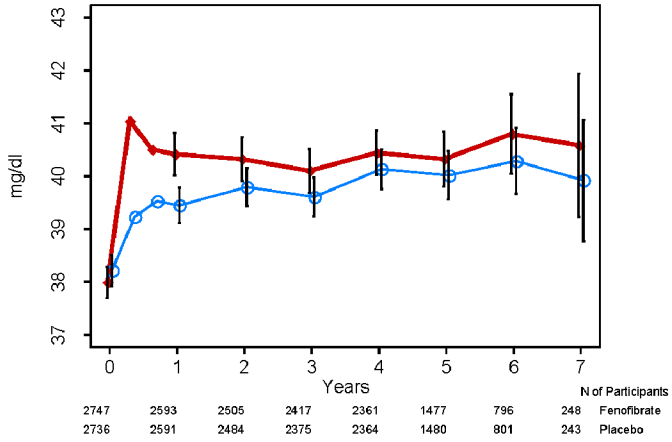
(A) Mean Total Cholesterol



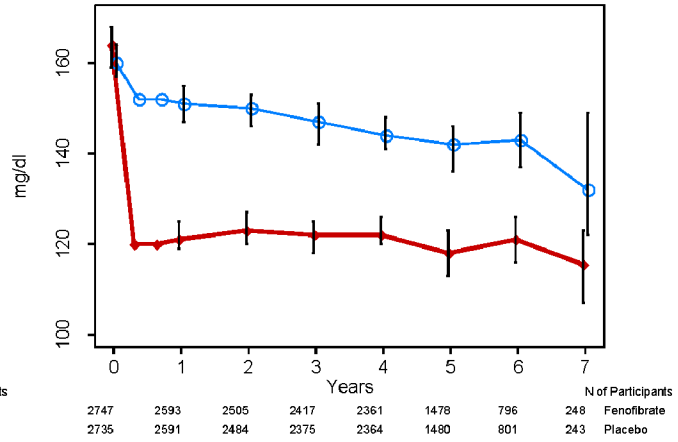

(B) Mean LDL-C




(C) Mean HDL-C



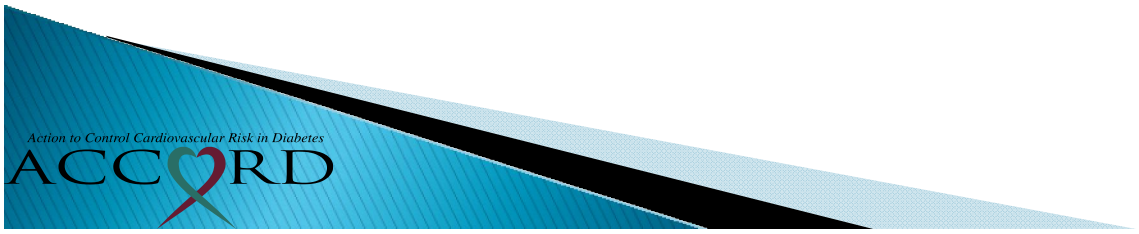

(D) Median Triglycerides




Action to Control Cardiovascular Risk in Diabetes
ACCORD

# Primary Outcome

| | Fenofibrate (N=2765) | | Placebo (N=2753) | | | |
|---|---|---|---|---|---|---|
| | N of Events | Rate (%/yr) | N of Events | Rate (%/yr) | HR (95% CI) | P Value |
| **Primary Outcome:** | | | | | | |
| Major Fatal or Nonfatal Cardiovascular Event | 291 | 2.24 | 310 | 2.41 | 0.92 (0.79 - 1.08) | 0.32 |



- Should we go further in managing diabetes using classical techniques?
  - *Probably not*
- Should we back away from current targets?
  - *No, but we need to individualize treatment.*
- Where are the opportunities?
  - *Screening to detect cases early*
  - *Simplifying therapy*
  - *Adherence*

# Diabetes Management: *The Big Picture*

| FOCUS | MEASUREMENT | GOAL | FREQUENCY |
|---|---|---|---|
| GLUCOSE | A1C | Less than 7.0% | Every 3-6 months |
| | Before meal, bedtime, and mid-sleep finger-prick glucose | 70-130 mg/dL | As needed to ensure control and to avoid hypoglyc. |
| | 1-2 hours after meal finger-prick glucose | <180 mg/dL | As needed to ensure control |
| BLOOD PRESSURE | Office blood pressure | <130/80 mm Hg | Every visit |
| CHOLESTEROL | Apolipoprotein B (ApoB-100) | <90 mg/dL (<80 mg/dL with vascular disease, smoking, fam hx early CAD, HTN) | Annually; more often while adjusting treatment |
| | -or- Non-HDL cholesterol (total cholesterol – HDL chol.) | <130 mg/dL (<100 mg/dL with vascular disease, smoking, fam hx early CAD, HTN) | |
| | -or- LDL cholesterol (requires fasting) | <100 mg/dL (<70 mg/dL with vascular disease, smoking, fam hx early CAD, HTN) | |
| | HDL cholesterol | >40 mg/dL (>50 mg/dL for women) | |
| | Triglycerides (requires fasting) | <150 mg/dL | |
| WEIGHT | BMI | 18.5-24.9 kg/m$^2$ (promote weight loss if ≥ 25) | Every visit |
| KIDNEY | Albumin-to-creatinine ratio; creatinine – estimated GFR | <30 mcg/mg; Stable (>60 mL/min/1.73m$^2$) | Annually |
| FEET | Complete exam | Can feel 10 gram filament, vibration testing, normal pulses, skin, structure, gait | Annually |
| EYE | Dilated eye exam | Normal | Annually |
| CVD | History and physical | No symptoms, aspirin if CVD or >40 or multiple risk factors, stress testing with symptoms | Every visit |
| DEPRESSION | Are you sad or blue? | Not usually | Every visit |
| TOBACCO | Medical history | None | Every visit |
| SEX | History | No concerns; contraception | Every visit |
| LIFESTYLE | History | Appropriate nutrition and physical activity | At diagnosis; at least annual update |
| DENTAL | History, exam | Exam (dentist), twice annual cleaning | Annually |
| EDUCATION | History | Understands all aspects of care | At diagnosis; annual update |
| GENERAL HEALTH | History | Vaccines, cancer screening, liver test (ALT), etc | Review at least annually |

Buse JB. Standards of Care. In: The Uncomplicated Guide to Diabetes Complications, 3rd edition. Pfeifer M, ed. American Diabetes Association,.

# Clinical Trials

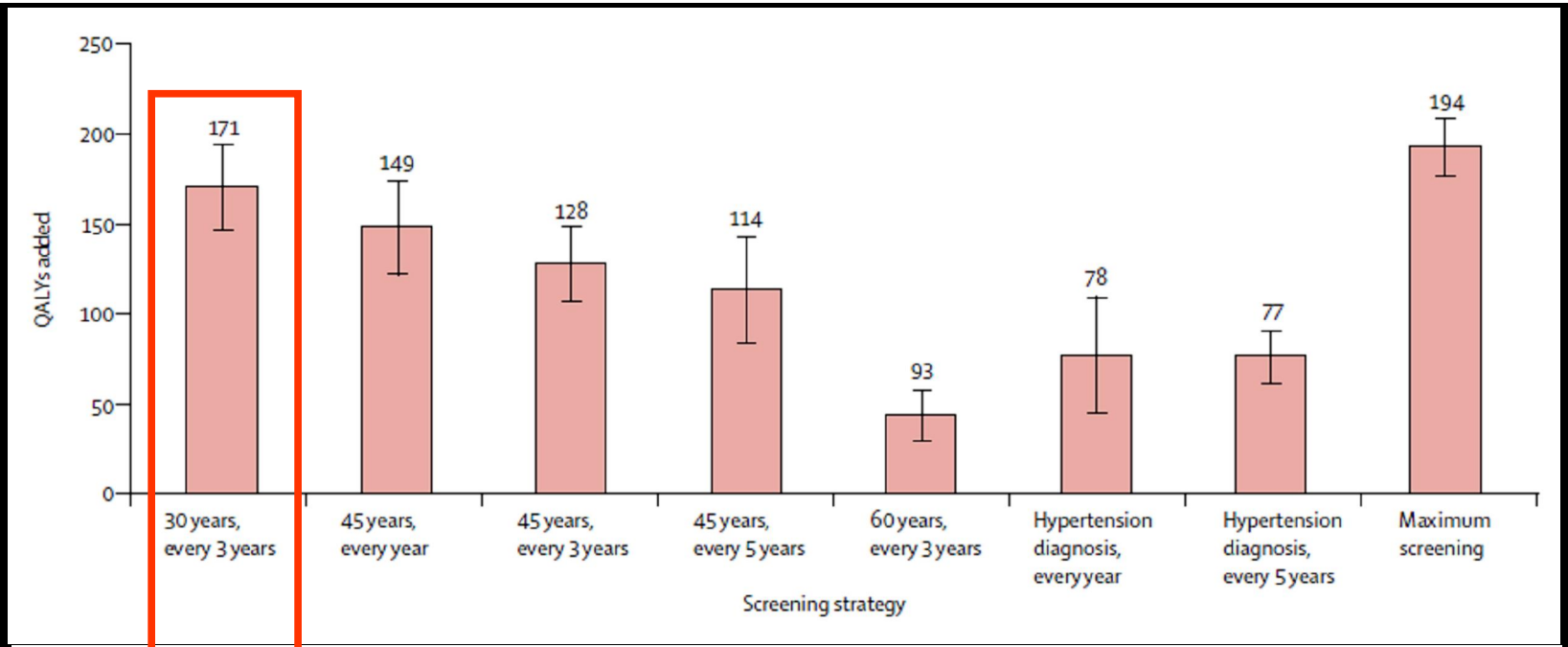
- Trials early in the natural history of disease show broad benefits
  - *UKPDS*
  - *DCCT*
- Trials later in the natural history of disease show less benefit
  - *VACSDM*
  - *ACCORD*
  - *ADVANCE*
  - *VADT*

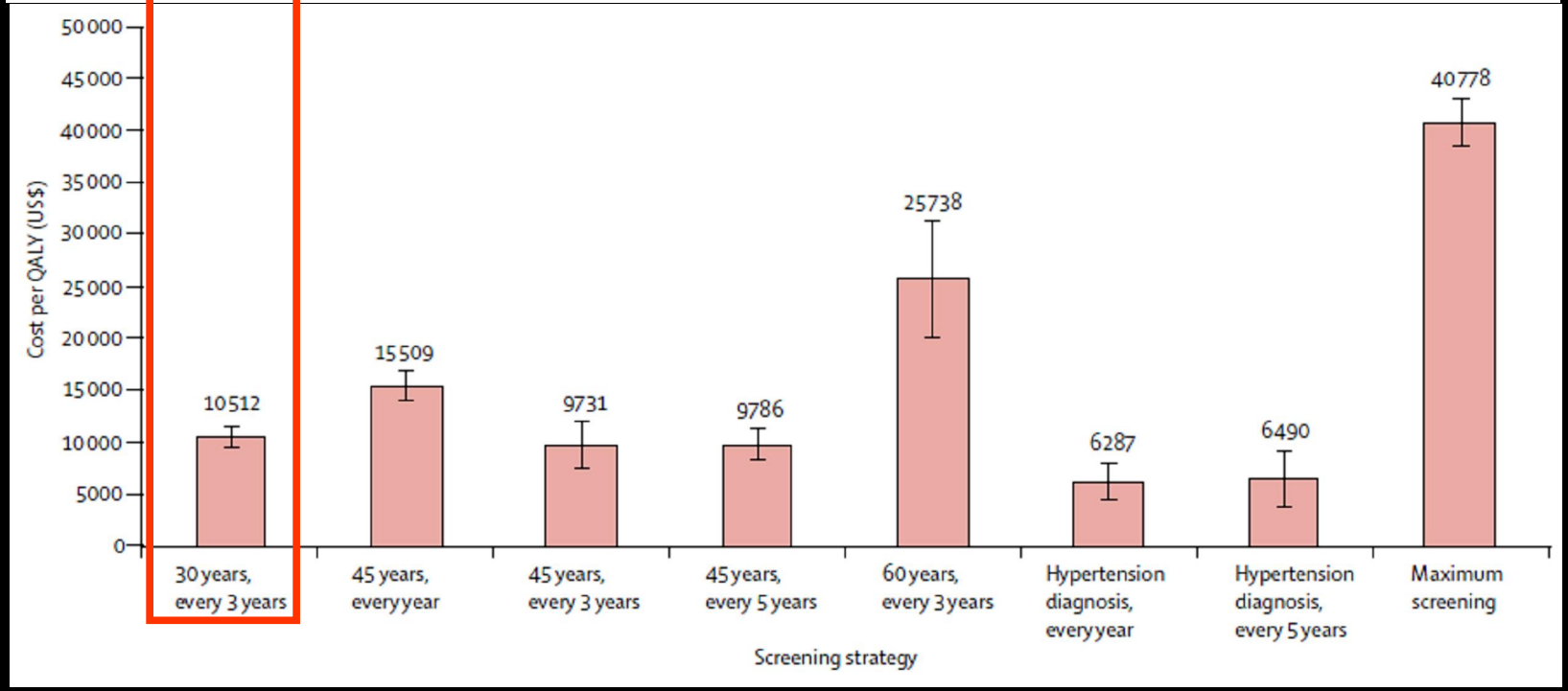
# Screening

- **Testing should be considered in all adults who are overweight (BMI 25 kg/m$^2$*) and have additional risk factors:**
  - ***physical inactivity***
  - ***first-degree relative with diabetes***
  - ***members of a high-risk ethnic population (e.g., African American, Latino, Native American, Asian American, Pacific Islander)***
  - ***women who delivered a baby weighing >9 lb or were diagnosed with GDM***
  - ***hypertension (≥140/90 mmHg or on therapy for hypertension)***
  - ***HDL cholesterol level <35 mg/dl (0.90 mmol/l) and/or a triglyceride level >250 mg/dl (2.82 mmol/l)***
  - ***women with polycystic ovary syndrome***
  - ***A1C ≥5.7%, IGT, or IFG on previous testing***
  - ***other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans)***
  - ***history of CVD***
- **In the absence of the above criteria, testing diabetes should begin at age 45 years**
- **If results are normal, testing should be repeated at least at 3-year intervals, with consideration of more frequent testing depending on initial results and risk status**

***At-risk BMI may be lower in some ethnic groups**

**ADA. *Diabetes Care* 2010;33 (S1): S11-S61**



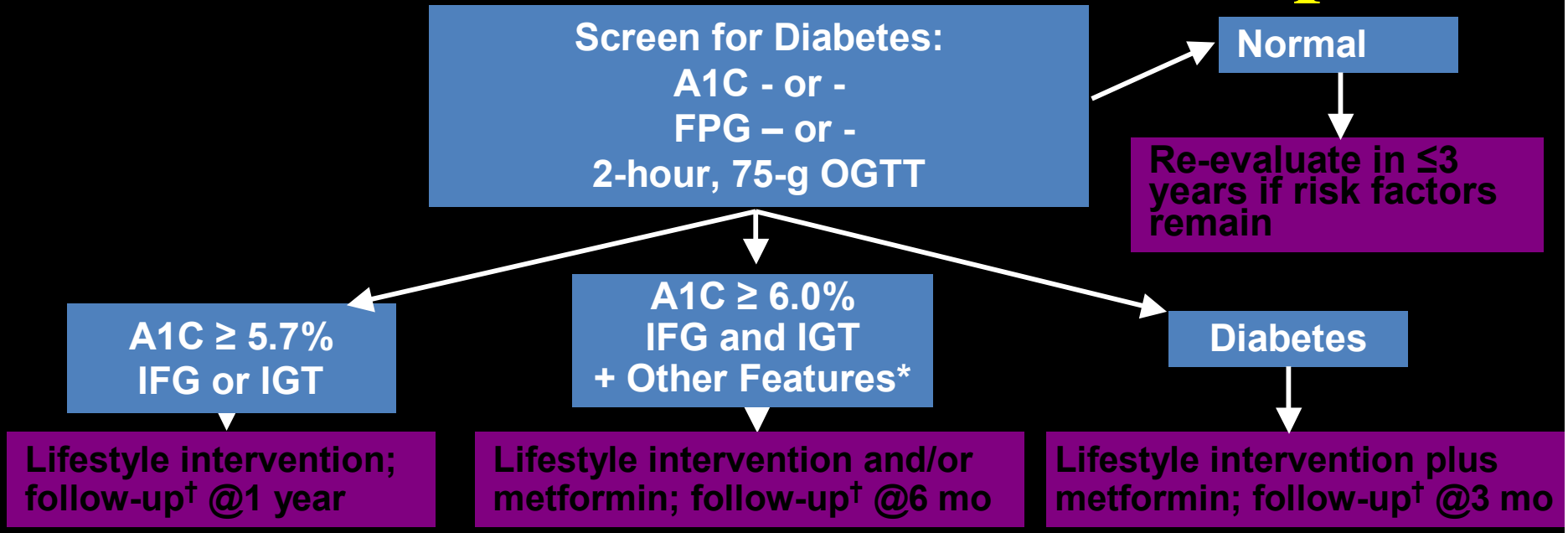

**Kahn RA, et al. Lancet 2010**

# HbA1c Advantages Compared with FPG, OGTT

- The HbA1c assay is standardized and aligned to DCCT/UKPDS
- Better index of overall glycemic exposure
- Equivalent in predicting risk for long-term complications
- Predicts CVD
- Substantially less laboratory variability
- Substantially less pre-analytic instability
- No need for fasting or timed samples
- Unaffected by acute (e.g. stress or illness-related) perturbations in glucose levels
- Used to guide management and adjust therapy

The International Expert Committee. *Diabetes Care* 2009; 32(7):1327-1334

# Screening and Diagnosis: Intervention and Follow-Up




- IFG: fasting (8 hours) plasma glucose 100-125 mg/dL
- IGT: 2-hour value in 75-g OGTT 140-199 mg/dL

† Follow-up here refers to formal reassesment of glycemic status. Follow-up should be individualized with respect to venue, frequency and goals.

* *"Other features": < 60 years old, BMI ≥ 30 kg/m$^2$ and either A1C > 6.0%, hypertension, low HDL, high triglycerides or family history of diabetes in first-degree relative*

- Diabetes: fasting ≥126 mg/dl or 2-hour ≥200 mg/dl; should be confirmed on a separate day unless unequivocally elevated and/or symptomatic

Adapted from American Diabetes Association. *Diabetes Care*. 2009;32(suppl 1):S13-S61.

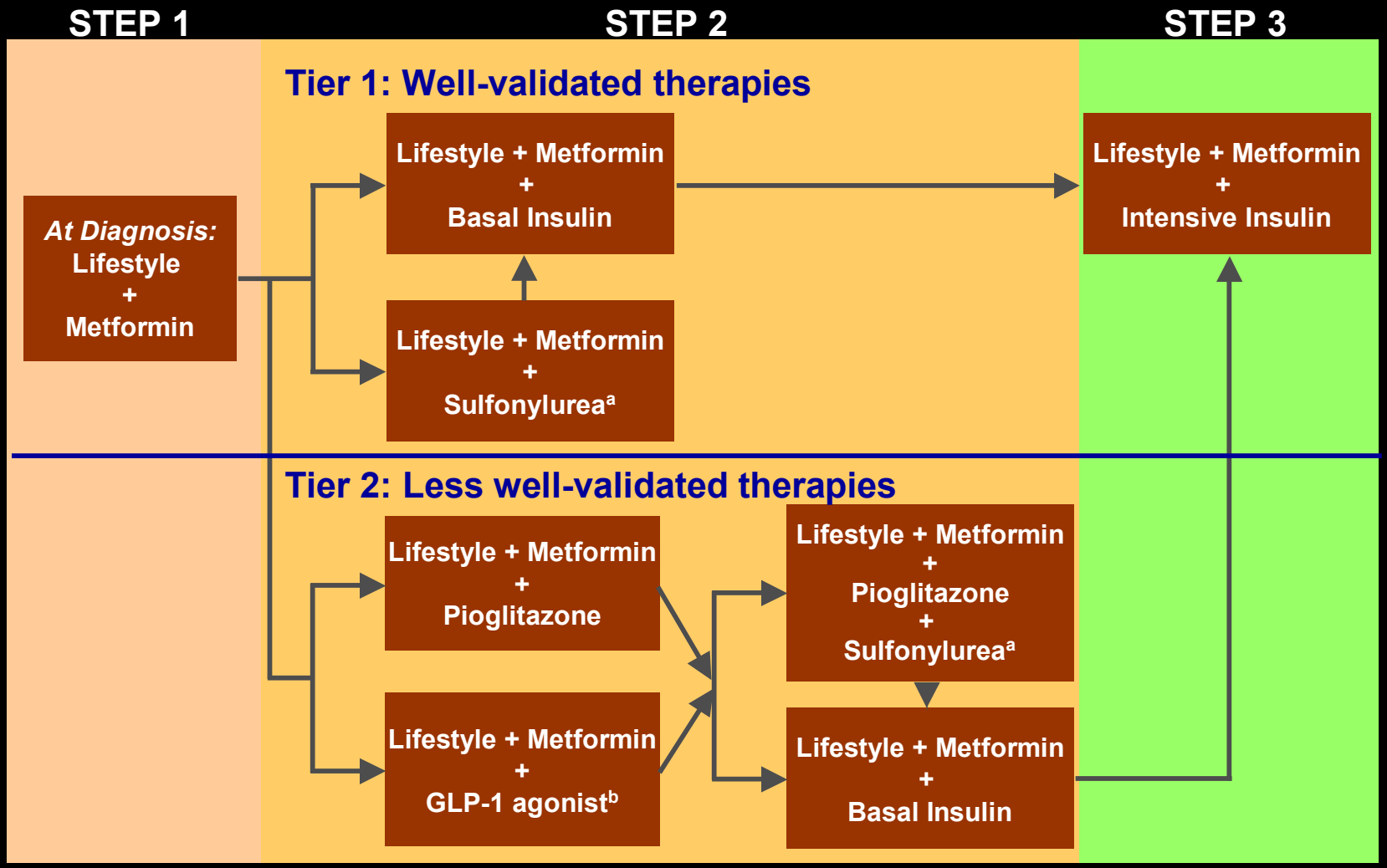
METFORMIN IS NOT FDA APPROVED FOR PREVENTION

# Antihyperglycemic Agents in Type 2 Diabetes

| Class | A1C Reduction | Severe Hypo-glycemia | Weight Change | CVD Risk Factor Improvement | Dosing (times/day) | Diabetes Comorbidity Contraindications |
|---|---|---|---|---|---|---|
| Metformin | 1.5 | No | Neutral | Minimal | 1-2 | Kidney, liver |
| NPH, Glargine, Detemir | 1.5 - 2.5 | Yes | Gain | TG | 1, Injected | None |
| R, Lispro, Aspart, Glulisine | 1.5 - 2.5 | Yes | Gain | TG | 1-4, Injected | None |
| Glipizide ER, Glimepiride | 1.5 | Yes | Gain | None | 1 | None |
| Pioglitazone | 0.5 - 1.4 | No | Gain | Lipids, BP | 1 | CHF, liver |
| Repaglinide | 1 - 1.5 | Yes | Gain | None | 3 | None |
| Nateglinide | 0.5 - 0.8 | Rare | Gain | None | 3 | None |
| Acarbose, Miglitol | 0.5 - 0.8 | No | Neutral | Minimal | 3 | None |
| Pramlintide | 0.5 – 0.9 | No | Loss | w/ weight loss | 3, Injected | None |
| Exenatide | 0.5 - 1.0 | No | Loss | w/ weight loss | 2, Injected | Kidney |
| Sitagliptin, saxagliptin | 0.6 - 0.8 | No | Neutral | Minimal | 1 | None |
| Colesevelam | ~0.5 | No | Neutral | LDL | 1-2 | Severe TG's |
| Bromocriptine QR | ~0.6 | No | Neutral | Minimal | 1 | None |
| Liraglutide | ~1.5 | No | Loss | BP, lipids | 1, injected | None |

Adapted from: Nathan DM, et al. *Diabetes Care*. 2009; 32:193-203. ADA. *Diabetes Care*. 2010;33:S11-S61. WelChol PI. 1/2008. Cycloset PI. 10/2010. Victoza PI. 1/2010.

# Updated ADA/EASD Consensus Algorithm




Reinforce lifestyle interventions at every visit and check A1C every 3 months until A1C <7.0%, then at least every 6 months thereafter. Change interventions whenever A1C ≥7.0%.

[a]Sulfonylureas other than glybenclamide (glyburide) or chlorpropamide.

[b]Insufficient clinical use to be confident regarding safety.

Nathan DM, et al. *Diabetes Care.* 2008;31:1-27

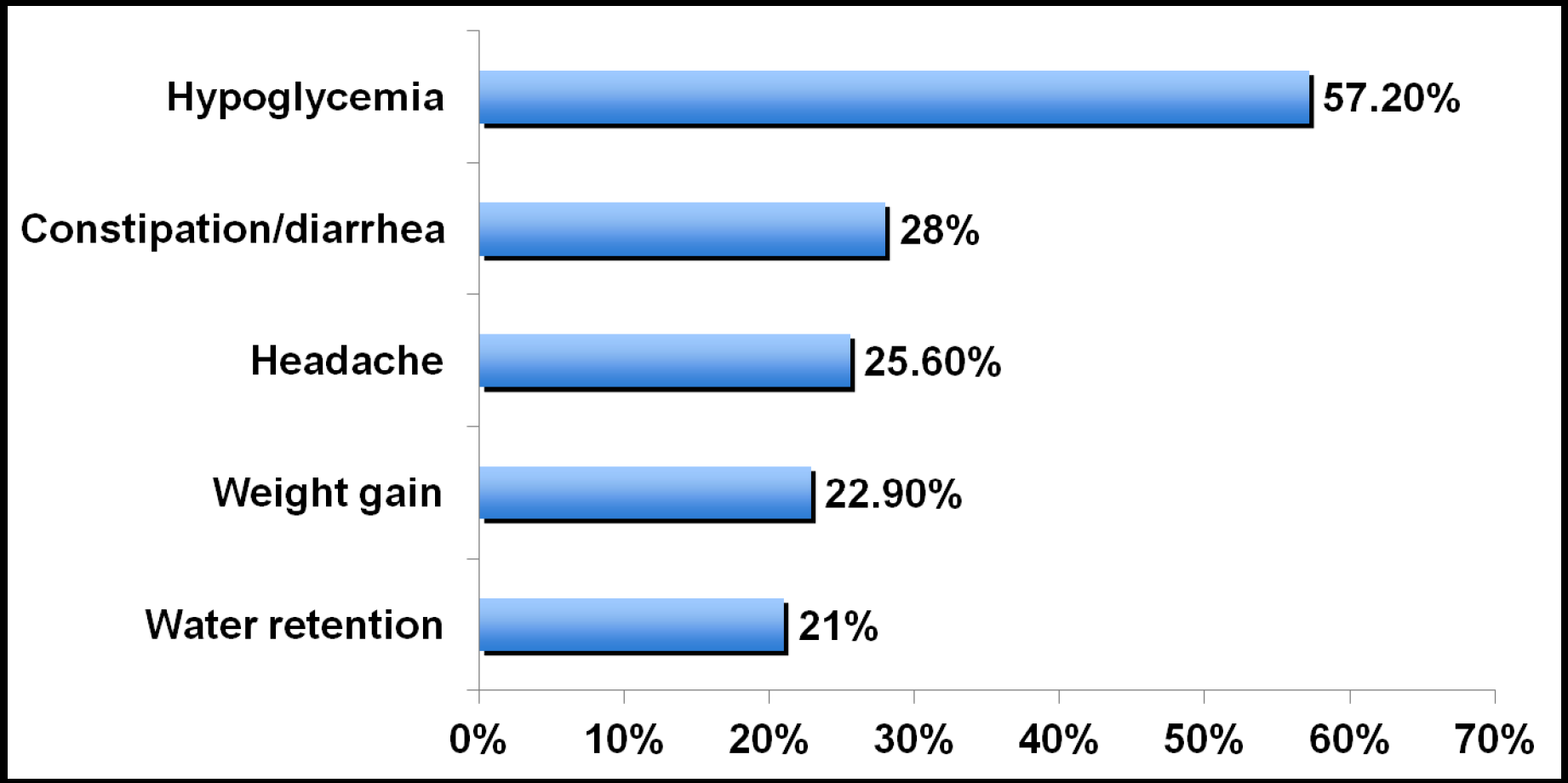
- Should we go further in managing diabetes using classical techniques?
  - *Probably not*
- Should we back away from current targets?
  - *No, but we need to individualize treatment.*
- Where are the opportunities?
  - *Screening to detect cases early*
  - *Simplifying therapy*
  - *Adherence*

# Factors Affecting Patient Adherence to Diabetes Medications

| Patient Belief/Concern | Odds Ratio for Poor Adherence | Confidence Interval |
|---|---|---|
| Feeling medicines are hard to take | 14.0 | 4.4ï 44.6 |
| Belief that they have diabetes only when sugar is high | 7.4 | 2ï 27.2 |
| No need to take medicine when glucose level was normal | 3.5 | 0.9ï 13.7 |
| Worry about side effects | 3.3 | 1.3ï 8.7 |
| Lack of self-confidence in controlling diabetes | 2.8 | 1.1ï 7.1 |

**Mann DM et al. *J Behav Med*. 2009;32(3):278–284.**

# Tolerability Issues Reported by Patients With Type 2 Diabetes



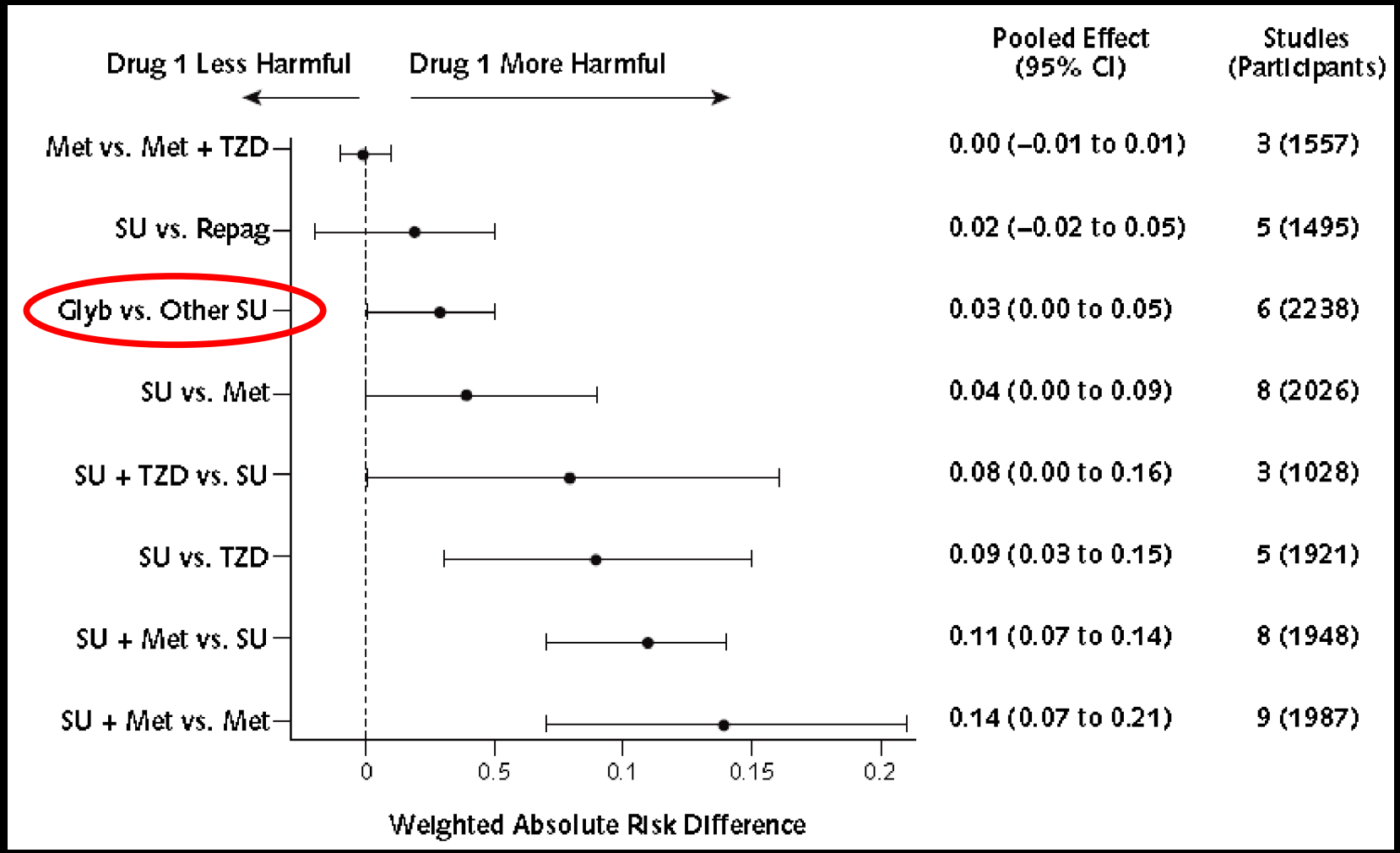

N = 2074 adults taking >1 oral antidiabetic drugs (OADs) but not insulin.
A majority (72%) experienced at least 1 tolerability issue in the past 2 weeks; 50% experienced >2.

Pollack MF et al. *Diabetes Res Clin Pract*. 2010;87(2):204–210.

# Optimizing Outcomes for Patients With Chronic Diseases

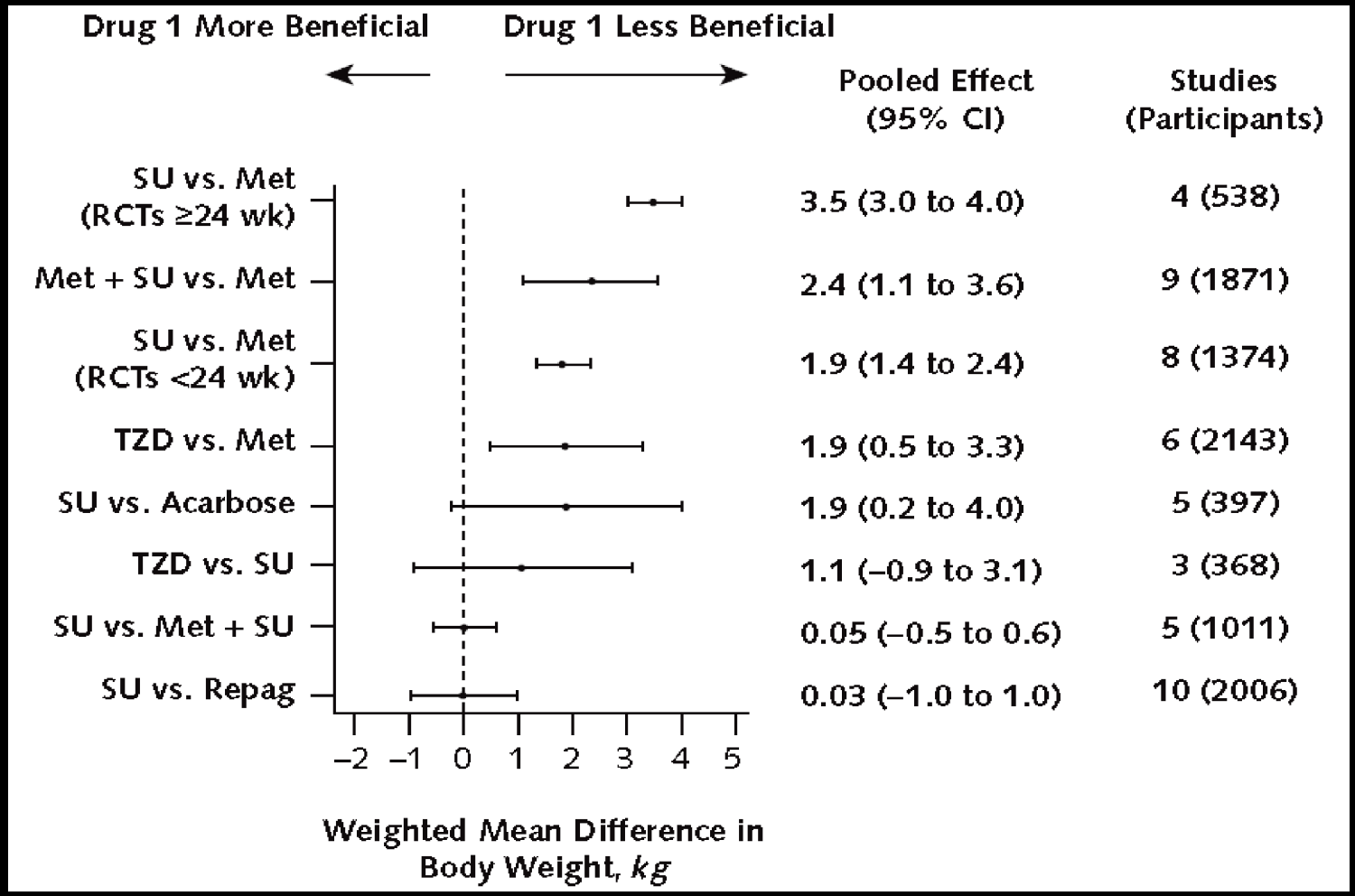
- Medication adherence rates in chronic care: 50%
  - Must have engaged, informed, motivated patient
  - Shared decision-making in a setting of mutual respect, open communication, cultural/ socioeconomic/educational sensitivity
  - Leverage opportunities to change/improve lifestyle behaviors

# Pooled Hypoglycemia Risk




Bolen S, et al. *Ann Intern Med*. 2007;147(6):386-399.

# Pooled Weight Gain Risk




Bolen S, et al. *Ann Intern Med*. 2007;147(6):386-399.

# The Problems With Weight Gain

- **Weight gain can be a barrier to intensifying treatment[1,2]**
  - **Approximately 50% of patients are very anxious about their weight[3]**
  - **Fear of the cosmetic effects of weight gain may outweigh the fear of long-term complications**
- **Weight gain results in increased CV risk factors**
  - **Obesity/weight gain is associated with dyslipidemia, hypertension, heart disease, and stroke[4,5]**

CV = cardiovascular.

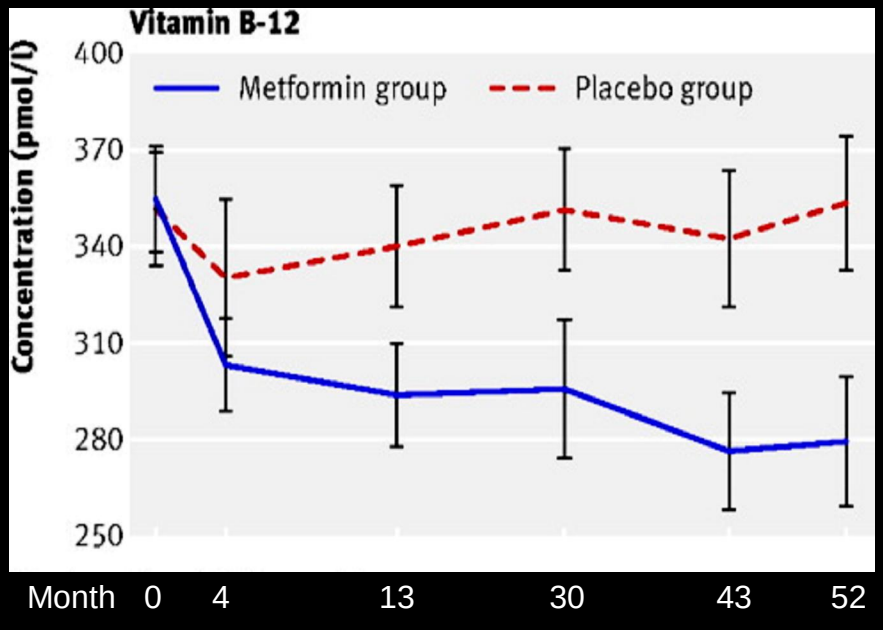
**1.** Davies M. *Int J Obesity.* 2004;28(suppl 2):S14ï S22. **2.** Korytkowski M. *Int J Obesity.* 2002;26(suppl 3): S18ï S24. **3.** Alberti G. *Pract Diab Int.* 2002;19(1):22ï 24a. **4.** WHO obesity fact sheet. www.who.int. **5.** Inzucchi SE. *JAMA.* 2002;287(3):360ï 372.

# Antihyperglycemic Agents in Type 2 Diabetes

| Class | Common side effects | Safety Concerns |
|---|---|---|
| | (other than hypoglycemia and weight gain) | |
| Metformin | GI | B12, lactic acidosis |
| NPH, Glargine, Detemir | Hypoglycemia, weight gain | Glargine – cancer |
| R, Lispro, Aspart, Glulisine | | |
| Glipizide ER, Glimepiride | | CVD, secondary failure |
| Pioglitazone | Fluid retention, weight gain | CHF, bone fractures, macular edema, bladder cancer |
| Repaglinide | Hypoglycemia, weight gain | Drug interactions |
| Nateglinide | | |
| Acarbose, Miglitol | GI | Hepatitis |
| Pramlintide | GI | |
| Exenatide | GI | Pancreatitis, renal failure, pancreatic/thyroid cancer |
| Sitagliptin, saxagliptin | | Pancreatitis, cancer |
| Colesevelam | GI | Hypertriglyceridemia, drug interactions |
| Bromocriptine QR | GI, rhinitis, fatigue | Concerns related to prior formulations |
| Liraglutide | GI | Pancreatitis, medullary thyroid cancer |

Adapted from: Nathan DM, et al. *Diabetes Care*. 2009; 32:193-203. ADA. *Diabetes Care*. 2010;33:S11-S61. WelChol PI. 1/2008. Cycloset PI. 10/2010. Victoza PI. 1/2010.

# Metformin and B12 Deficiency




- Absolute risk of B12 deficiency (<150 pmol/L) is 7.2% higher with metformin.
- Absolute risk of low B12 (150-220 pmol/L) is 11.2% higher with metformin.
- "Our findings suggest that regular measurement of vitamin B-12 concentrations during long term metformin treatment should be strongly considered."
- Other studies suggest that calcium supplements can prevent this effect

De Jager J, et al. BMJ. 2010 May 20;340:c2181. doi: 10.1136/bmj.c2181.

# Metformin and Renal Insufficiency

- Can increase incidence of lactatemia in type 2 diabetic patients without renal dysfunction
  - creatinine, alanine transferase and BMI are independent associated factors of blood lactic acid levels
- Alternative approach to PI recommendation to avoid metformin in men with creatinine >1.3 mg/dl and in women >1.4 mg/dl:
  - Avoid use in stage 4, stage 5 CKD
  - Use with caution (perhaps ½ max dose) in stage 3 CKD
  - No restrictions in stage 1, 2 CKD

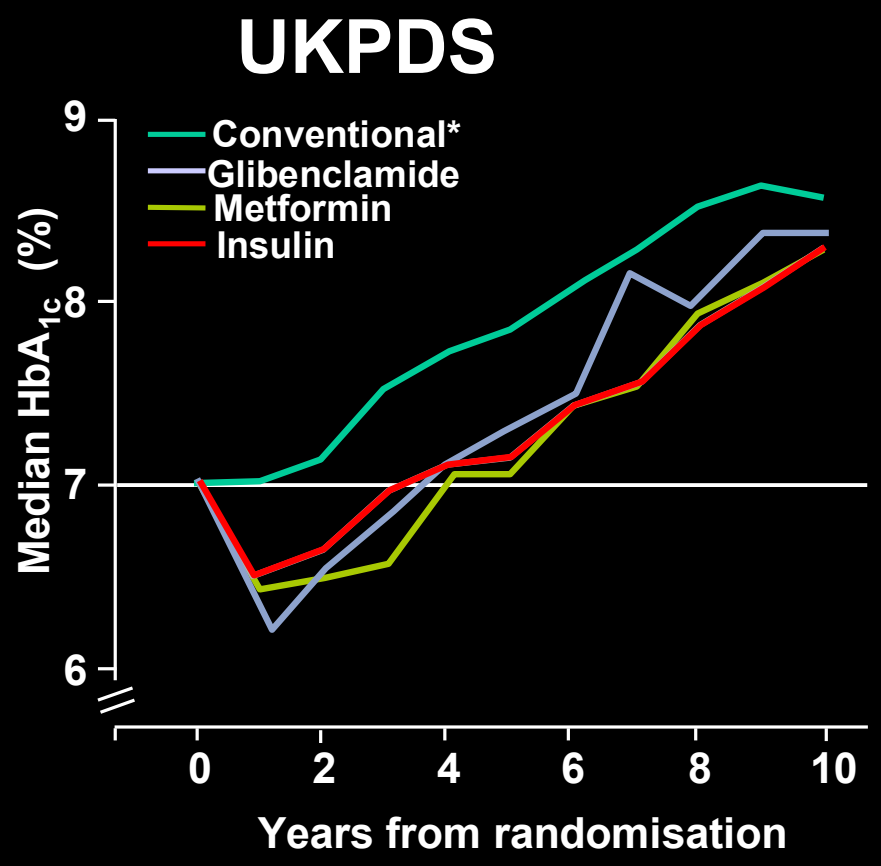
Liu F, et al *Chin Med J* (Engl) 2009;122:2547-2553.
Shaw JS, et al. Diabetic Medicine 24:1160-3, 2007.

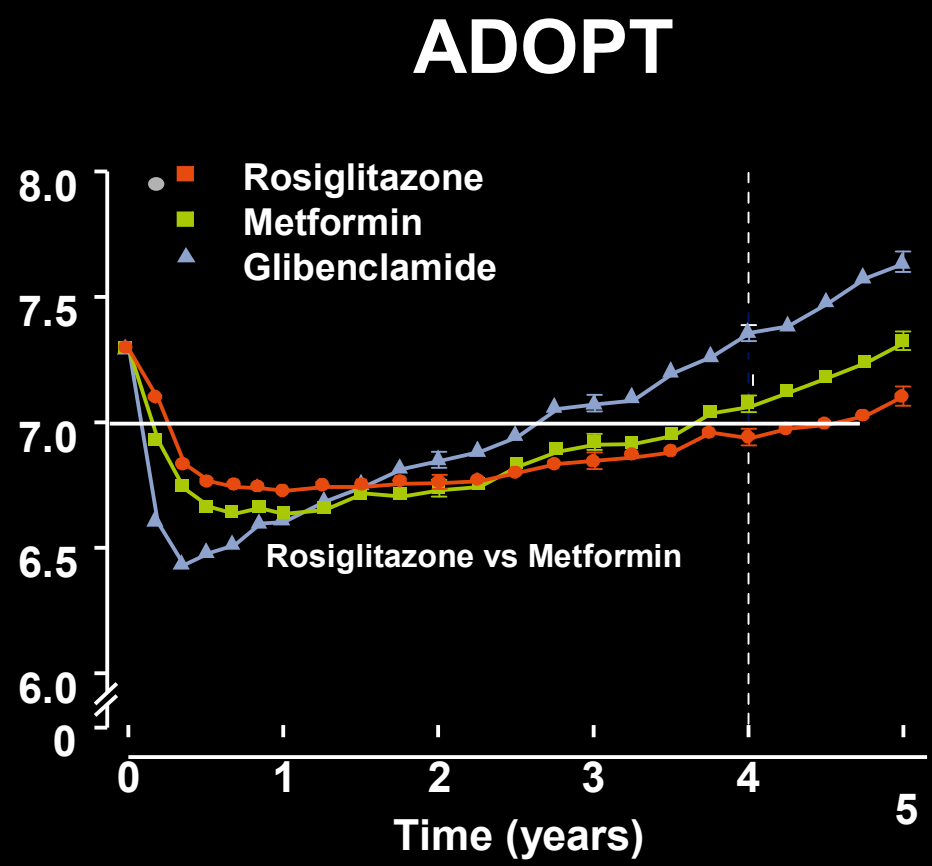
# Sulfonylureas and Increased CV Risk

- University Group Diabetes Program (UGDP) some increased risk was seen[1]
- In UKPDS and ADVANCE, sulfonylureas themselves were not associated with the risk of diabetes-related death or myocardial infarction[2,3]
- Short-term oral sulfonylurea therapy safe and in most patients with diabetes due to SUR1 mutations – may replace treatment with insulin injections[4]


1. *Diabetes* 1976; 25:1129-1153
2. *Lancet* 1998; 12:352
3. *N Engl J Med* 2008; 358:2560-72
4. *Diabetes Care* 2008; 31:204-209

# Over Time . . .
# Glycemic Control Deteriorates




UKPDS 34. Lancet 1998:352:854–865; Kahn et al, (ADOPT), NEJM 2006;355(23):2427-43.

*Diet initially then sulphonylureas, insulin and/or metformin if FPG > 15 mmol/l; †ADA clinical practice recommendations. n=5102

# Pioglitazone: Heart Failure

| PROactive[1] | Pioglitazone (n = 2605) | | Placebo (n = 2633) | | |
|---|---|---|---|---|---|
| | Number of Events | Number of Patients (%) | Number of Events | Number of Patients (%) | *P* Value |
| Any report of heart failure | 417 | 281 (11%) | 302 | 198 (8%) | < 0.0001 |
| Heart failure not needing hospital admission | 160 | 132 (5%) | 117 | 90 (3%) | 0.003 |
| Heart failure needing hospital admission | 209 | 149 (6%) | 153 | 108 (4%) | 0.007 |
| Fatal heart failure | 25 | 25 (1%) | 22 | 22 (1%) | 0.634 |

- Data indicate a 16% decreased risk of nonfatal myocardial infarction, death from any cause, or stroke for pioglitazone compared to placebo[1]
- Because of possible fluid retention, thiazolidinediones are not recommended in any patient with symptomatic heart failure and contraindicated in any patient with class III-IV heart failure[2]
- Thiazide-type diuretics, but not loop diuretics, are effective in controlling fluid retention with glitazone use[3]

1.Dormandy JA, et al. *Lancet.* 2005;366:1279-1289.
2.US Food and Drug Administration Web site. http://www.fda.gov/Cder/drug/InfoSheets/HCP/pioglitazoneHCP.htm. Accessed 9/24/2008.
3.Karalliedde J, et al. *J Am Soc Nephrol.* 2006;17:3482-3490.

# Pioglitazone: Increased Fracture Risk in Women

| Therapy | Fracture Rate per 100 person-years | Relative Risk |
|---|---|---|
| Pioglitazone | 1.9 | 1.7 |
| Placebo or active comparator | 1.1 | |

- Meta-analysis of fracture AEs for clinical trials of pioglitazone
  - Pio = 8,100; Comparison = 7,400 (12,000 person-years per group)
- Increased risk in women but not men

Takeda Letter to Healthcare Providers 2007.

# *Diabetologia* On-Line June 26, 2009

**Risk of malignancies in patients with diabetes treated with human insulin or insulin analogues: a cohort study**

L. G. Hemkens · U. Grouven · R. Bender · C. Günster · S. Gutschmidt · G. W. Selke · P. T. Sawicki

**Insulin glargine use and short-term incidence of malignancies—a population-based follow-up study in Sweden**

J. M. Jonasson · R. Ljung · M. Talbäck · B. Haglund · S. Gudbjörnsdòttir · G. Steineck

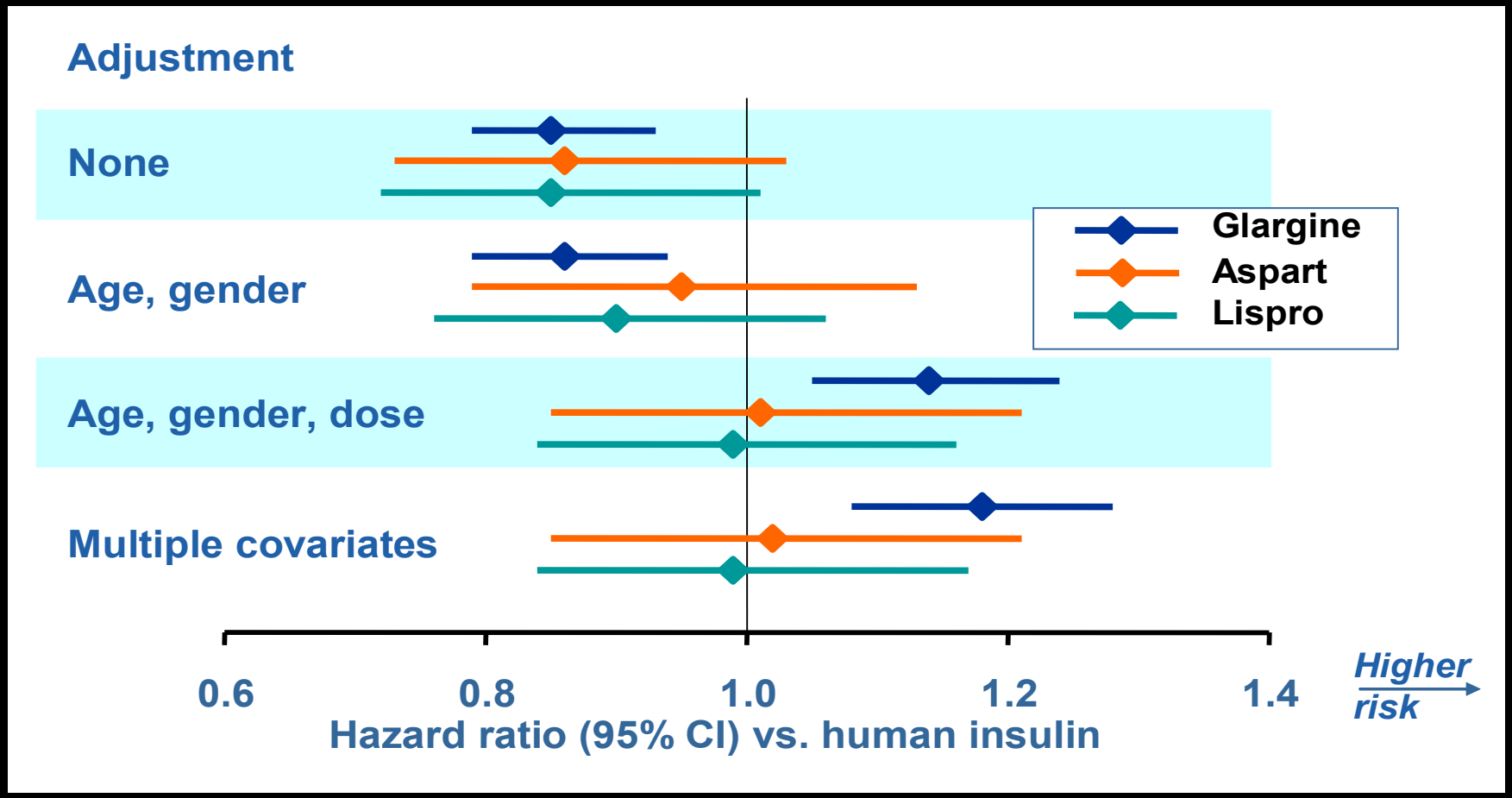
**Use of insulin glargine and cancer incidence in Scotland: a study from the Scottish Diabetes Research Network Epidemiology Group**

H. M. Colhoun · SDRN Epidemiology Group

**The influence of glucose-lowering therapies on cancer risk in type 2 diabetes**

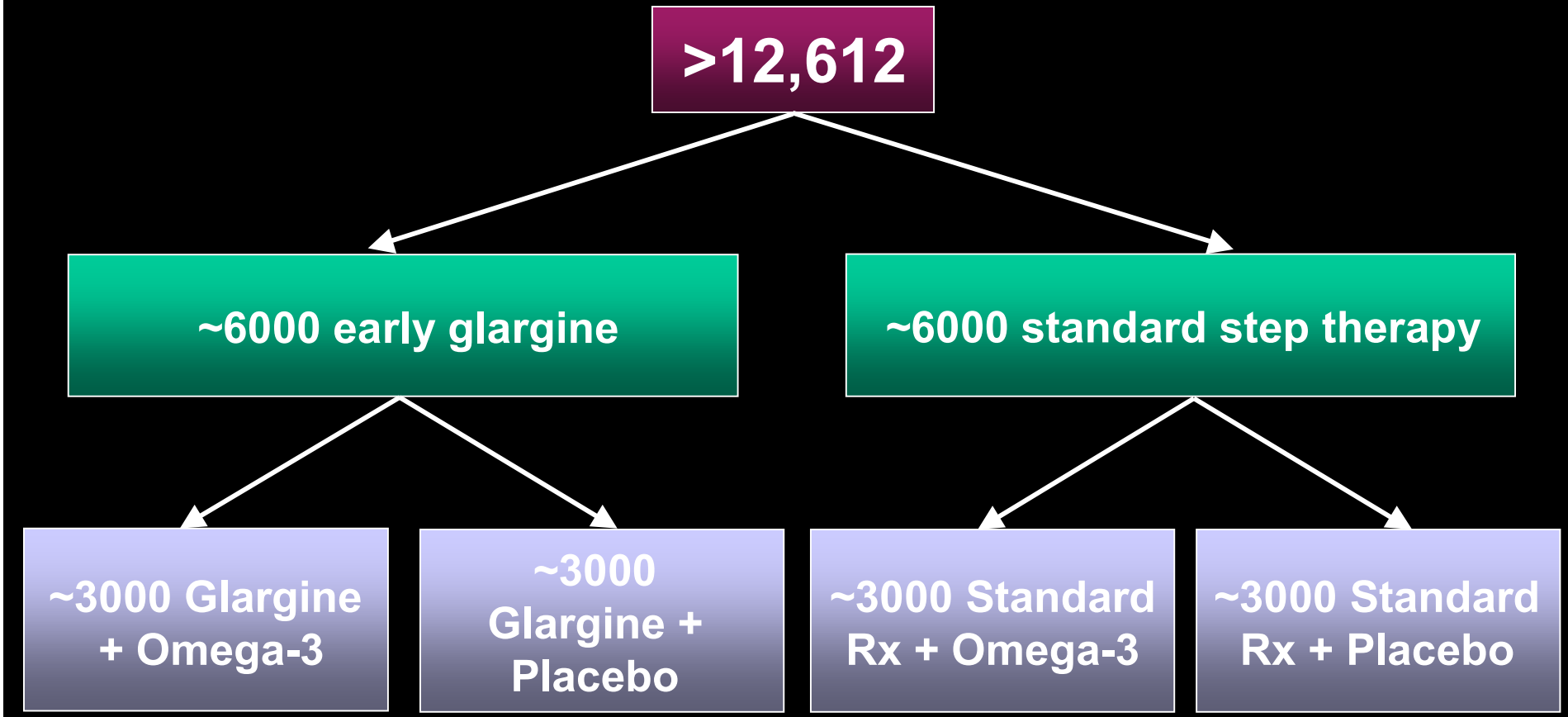
C. J. Currie · C. D. Poole · E. A. M. Gale

# Hazard Ratios for Risk of All Forms of Cancer after Various Adjustments




Hemkens et al. *Diabetologia* 2009; 50:1732-1744

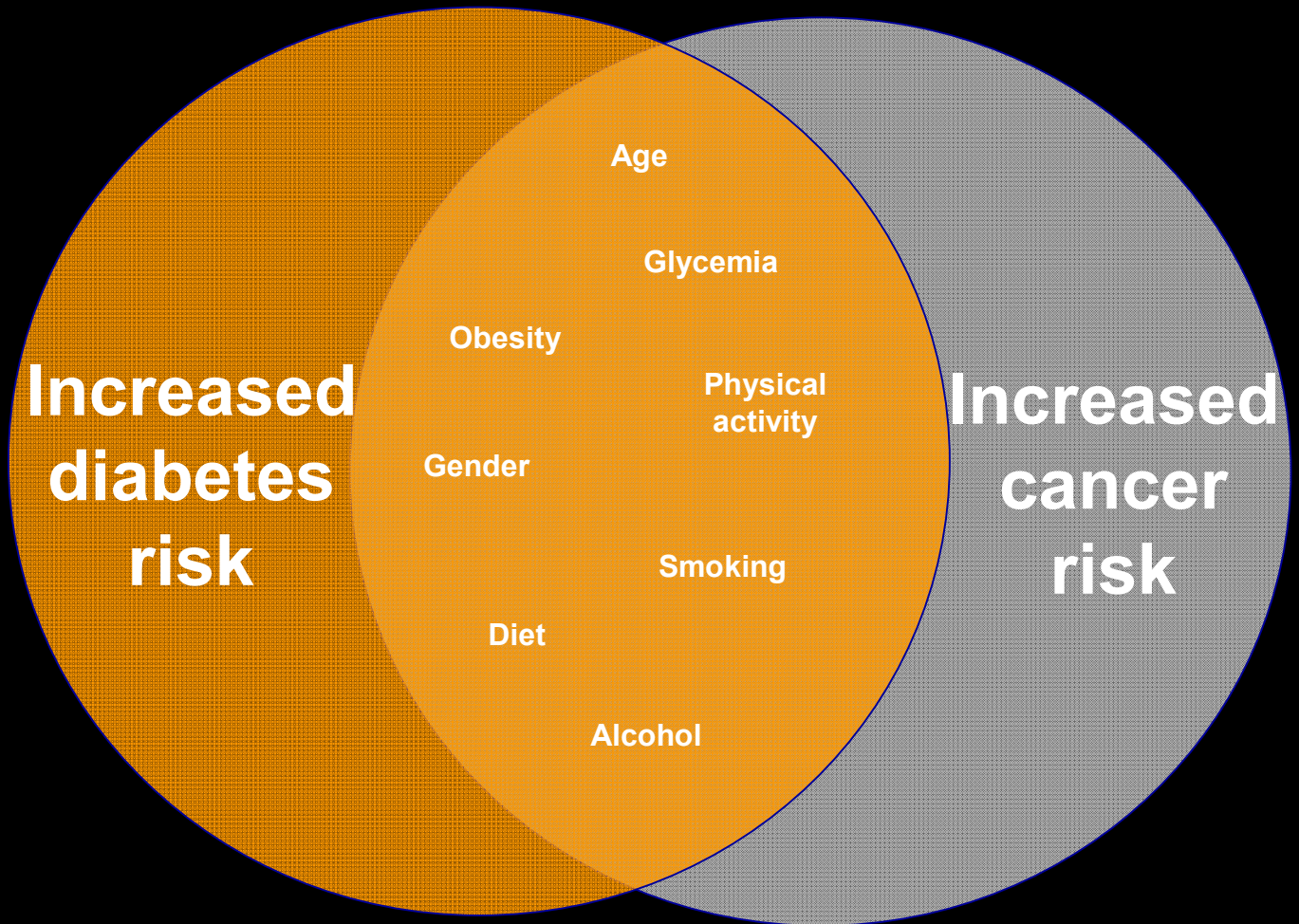
# ORIGIN STUDY DESIGN




*Gerstein HC, et al. Am Heart J. 2008;155:26–32.*

# Common Risk Factors for Diabetes and Cancer

## ADA Consensus Report on Diabetes and Cancer




Giovannucci E et al. *Diabetes Care* 2010;33:1674-85.

# Pooled Hazard Ratios of Long-term, All-Cause Mortality in Cancer Patients With & Without Diabetes Mellitus in Selected Cancer Sites

| Cancer Site | Studies (Estimates), No. | Total Patients, No. | Patients With Diabetes, No. | Pooled HR (95% CI)[a] |
|---|---|---|---|---|
| Endometrial | 4 (4)[40,42,46,48] | 2900 | 429 | 1.76 (1.34-2.31) |
| Breast | 4 (4)[40,41,43,45] | 13 019 | 1107[b] | 1.61 (1.46-1.78) |
| Prostate | 3 (3)[37,40,47] | 6264 | 555[b] | 1.51 (0.94-2.43) |
| Gastric | 3 (3)[37,40,50] | 6200 | 687[b] | 1.36 (0.92-2.01) |
| Colorectal | 6 (7)[33,34,36,37,39,40] | 54 740 | 8028[b] | 1.32 (1.24-1.41) |
| Hepatocellular | 3 (5)[30,37,44] | 3724 | 848[b] | 1.30 (0.99-1.70) |
| Lung | 4 (5)[29,37,38,40] | 11 109 | 989[c] | 1.15 (0.99-1.34) |
| Pancreas | 4 (4)[28,37,40,49] | 1681 | 477[b] | 1.09 (0.70-1.69) |

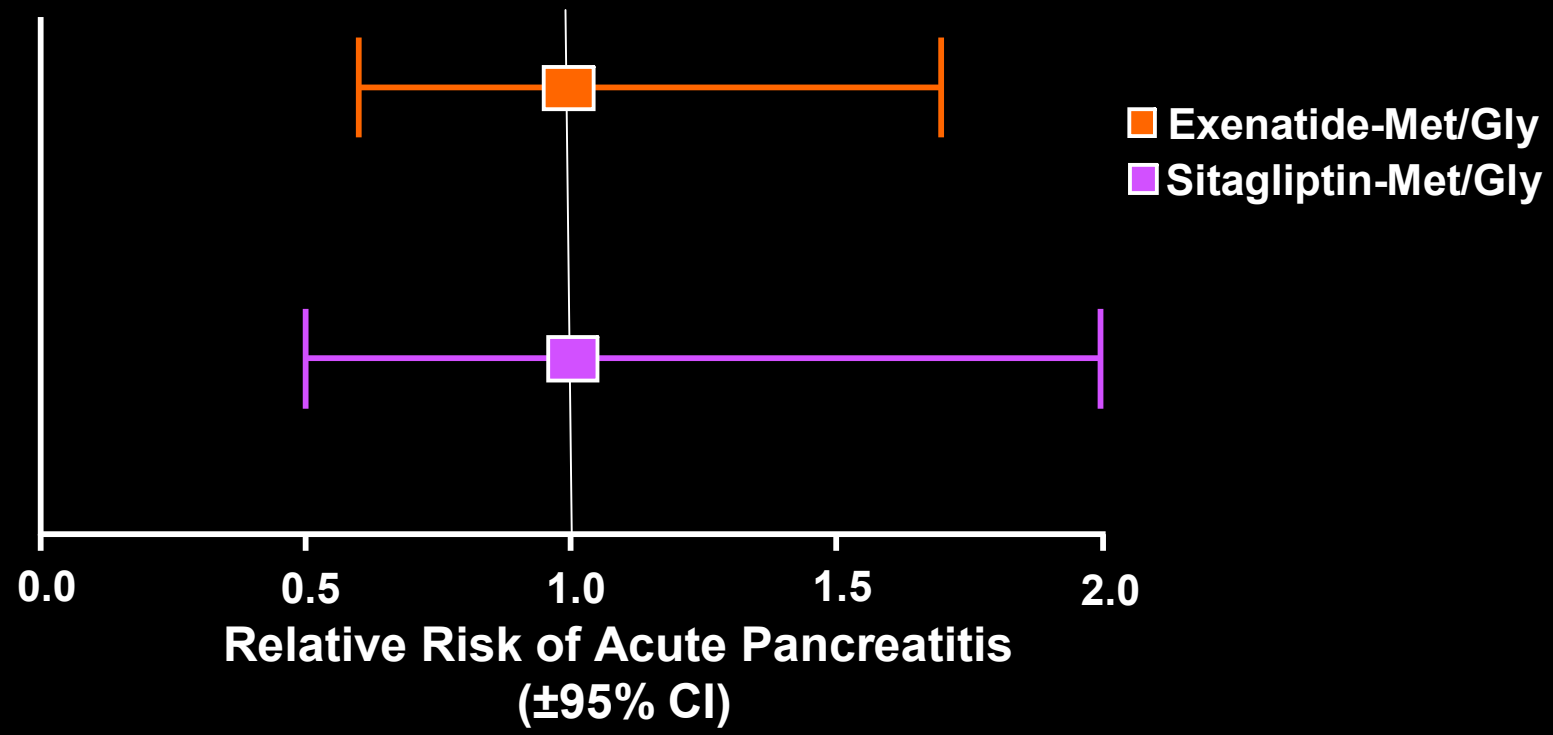
Barone, B. B. et al. *JAMA* 2008;300:2754-2764.

# "Increased incidence of pancreatitis and cancer among patients given GLP-1 based therapy"[1]

- Examined FDA reported adverse events (AERS) with sitagliptin and exenatide from 2004-2009
- "Use of sitagliptin or exenatide increased the odds ratio for pancreatitis 6-fold, compared with other therapies. . . . Pancreatic cancer was more commonly reported among patients that took sitagliptin or exenatide, compared with other therapies. . . . All other cancers occurred more frequently among patients that took sitagliptin, compared with other therapies."[1]
- Major methodological flaws. "AERS cannot be used to calculate the incidence of an adverse event in the U.S. population."[2]


1. Elashoff M, et al. Gastroenterology. Available on line… 3/1/2011
2. http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm, accessed 3/1/2001

# Acute Pancreatitis With Antidiabetic Agents in Human Subjects




- The absolute risk of acute pancreatitis was comparable among initiators of exenatide and sitagliptin

  Drug Pair 1: Exenatide 0.13% (N = 27,996); Met/Gly 0.13% (N = 27,983)
  Drug Pair 2: Sitagliptin 0.12% (N = 16,267); Met/Gly 0.12% (N = 16,281)

Dore D et al. *Curr Med Res Opin*. 2009;25(4):1019ï 1027.

# Use of GLP-1 Agonists in T2DM Patients with Renal Impairment

- Currently limited experience beyond mild-stage renal disease
- Liraglutide:
  - Available pharmacokinetic data suggests that T2DM patients with renal insufficiency can use standard treatment regimens
- Exenatide:
  - In patients with stage 1 or 2 chronic kidney disease, appropriate to administer exenatide without dosage adjustment, as tolerated
  - Poor tolerability and significant changes in PK make the currently available therapeutic doses (5 and 10 micrograms) unsuitable in stage 4 or 5 CKD.

Jacobsen LV, et al. *Br J Clin Pharmacol*. 2009 Dec;68(6):898-905.
Linnebjerg H, et al. Br *J Clin Pharmacol*. 2007 Sep;64(3):317-27.

# Liraglutide: Black Box Warning

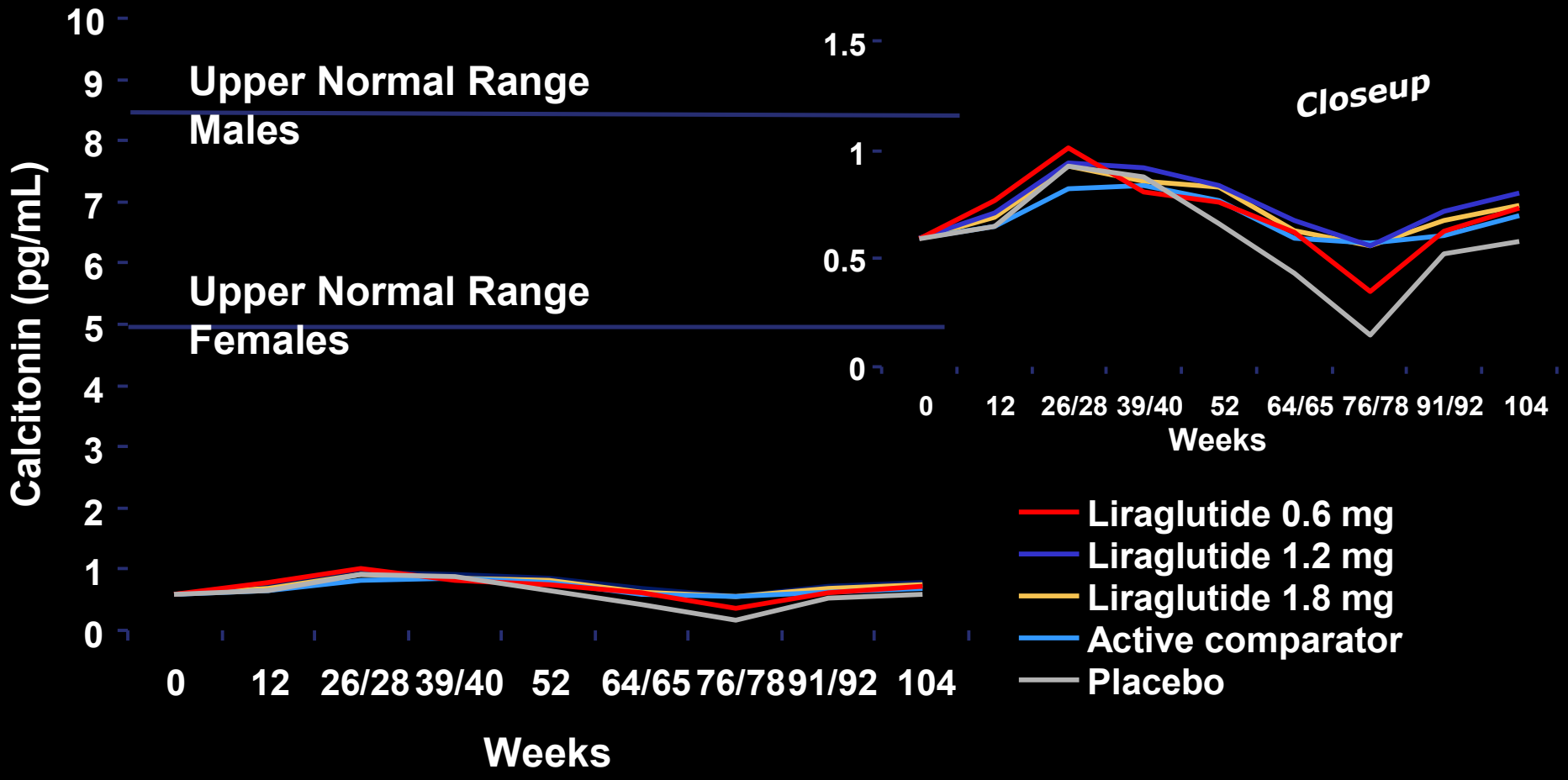
**Warning: risk of thyroid C-cell tumors**

- **Liraglutide causes thyroid C-cell tumors at clinically relevant exposures in *rodents***
- **Unknown whether it causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans**
  - **Human relevance could not be determined by clinical or nonclinical studies**
- **Contraindicated in patients with:**
  - **Multiple endocrine neoplasia syndrome type 2 (MEN 2)**
  - **Personal or family history of MTC**

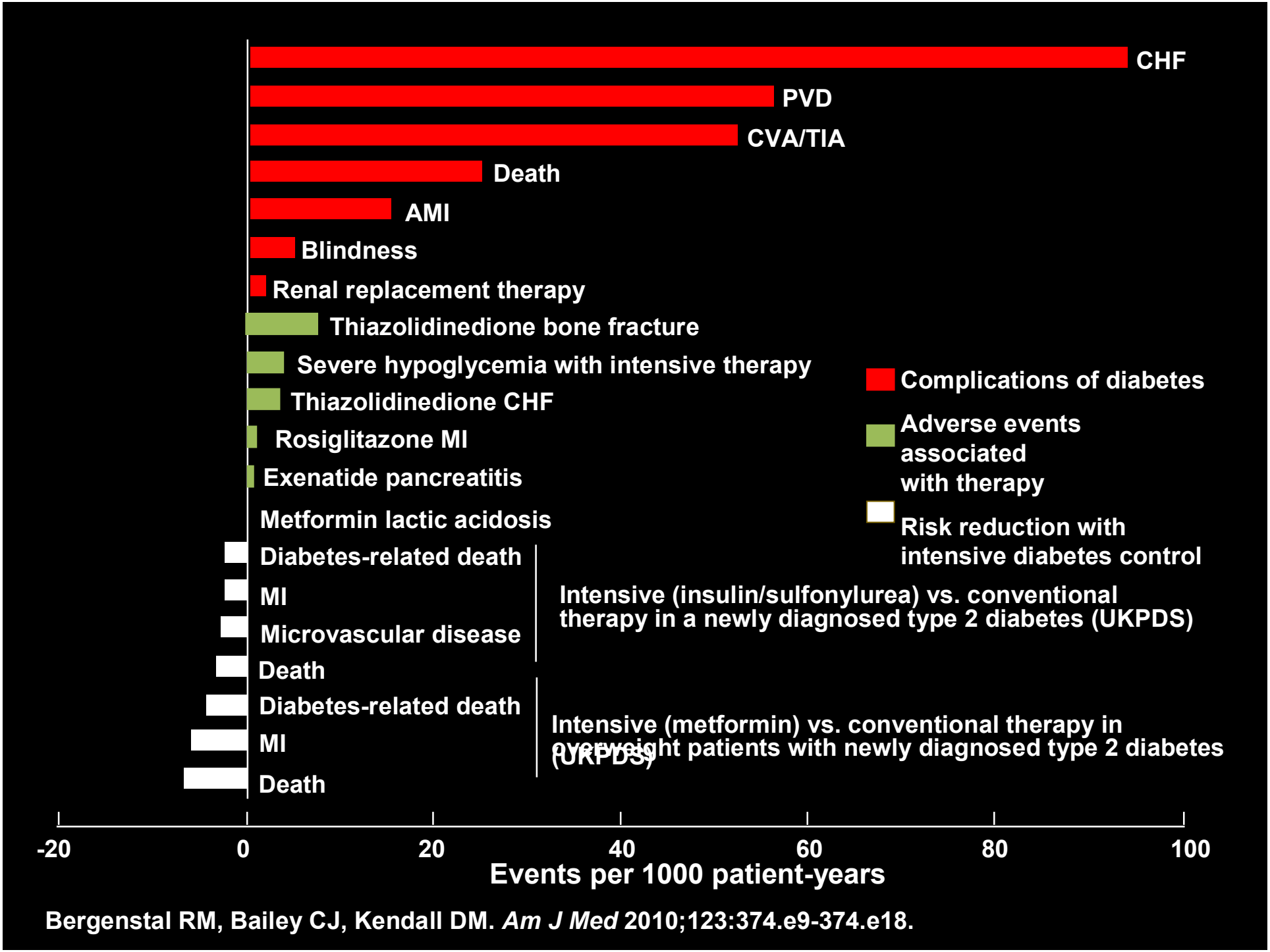
**Prescribing information, 2010**

# Calcitonin Levels Observed in LEAD Studies of Liraglutide in Human Diabetes

**Compared to variations during study (see placebo-curve), differences between comparators are extremely small and far within normal ranges**




Hegedus L, et al. J Clin Endocrinol Metab. 2011 Jan 5. [Epub ahead of print]

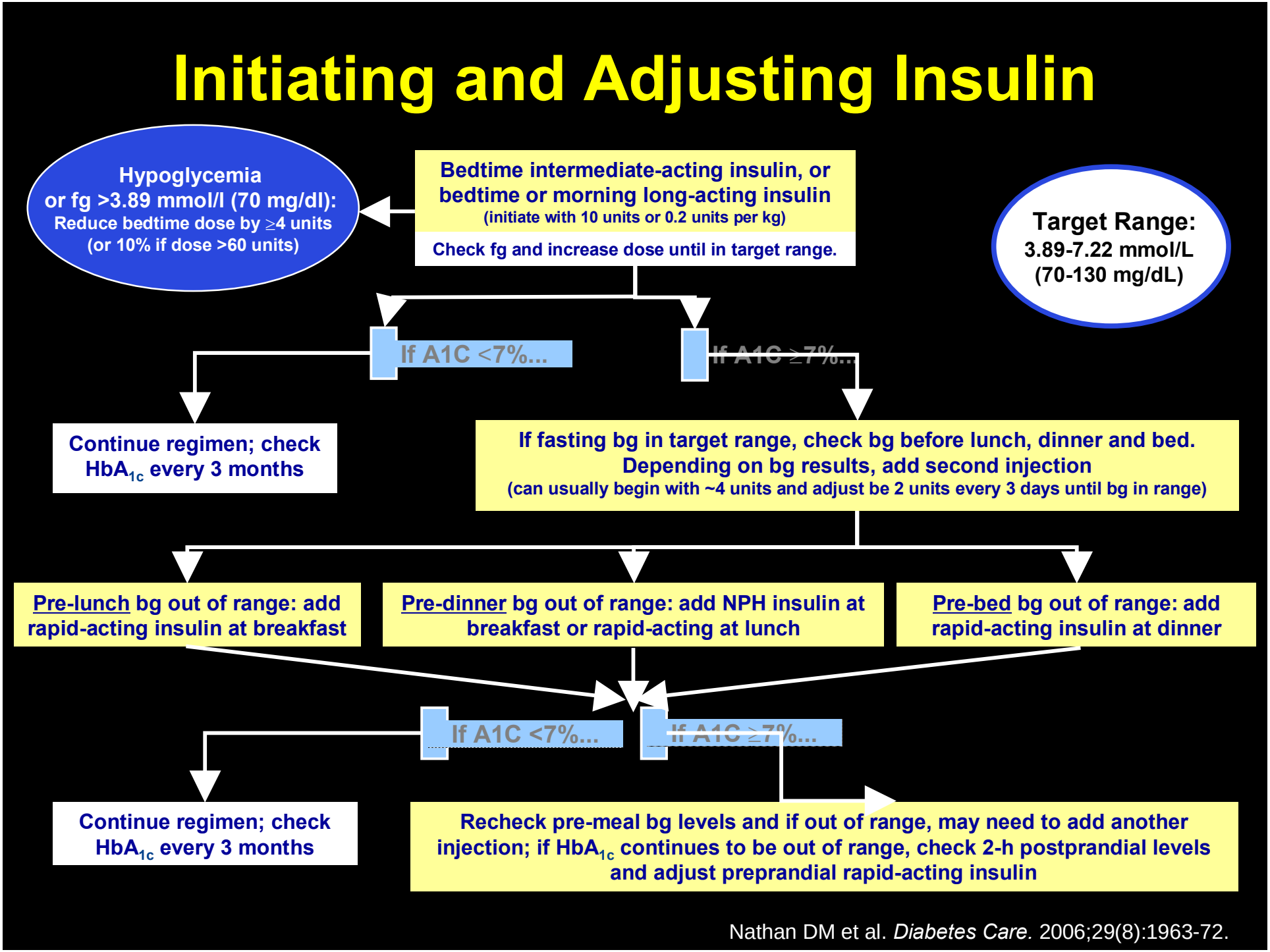



Bergenstal RM, Bailey CJ, Kendall DM. *Am J Med* 2010;123:374.e9-374.e18.

# Diabetes Drug Safety and Development: What Have we Learned?

- Drug safety MUST be assessed in the context…
  - …of potential risk/benefit of other agents
  - …of inherent risks of diabetes and hyperglycemia
- Glycemic control in diabetes
  - must remain central focus of management
  - limited by adherence, efficacy, safety, adverse effects, hypoglycemia
- We must not forget the past
  - phenformin → metformin
  - cerivastatin vs other statins
  - troglitazone → rosiglitazone → pioglitazone

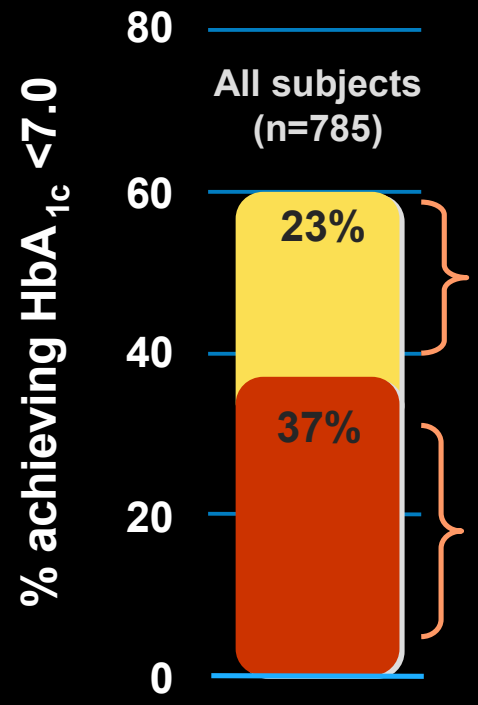
# Initiating and Adjusting Insulin



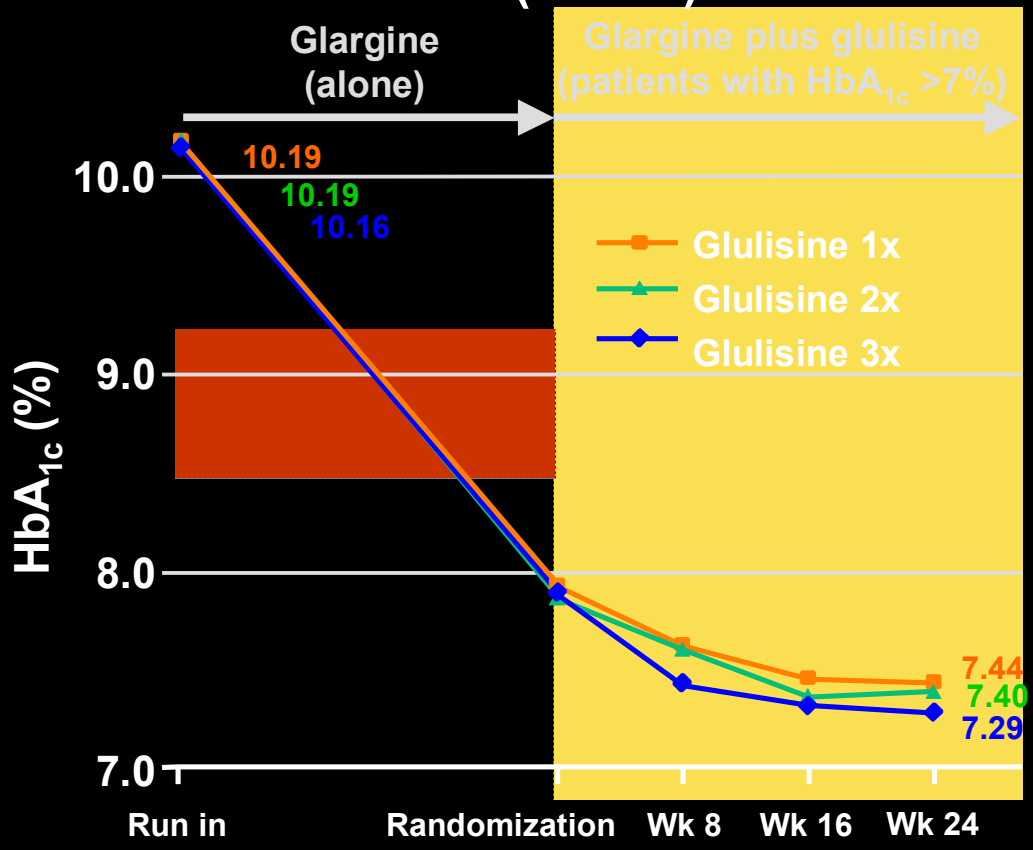

Nathan DM et al. *Diabetes Care.* 2006;29(8):1963-72.

# 1.2.3 Study: Glargine Plus 1, 2 or 3 Doses of Glulisine

## Responders in the whole population (n=785)



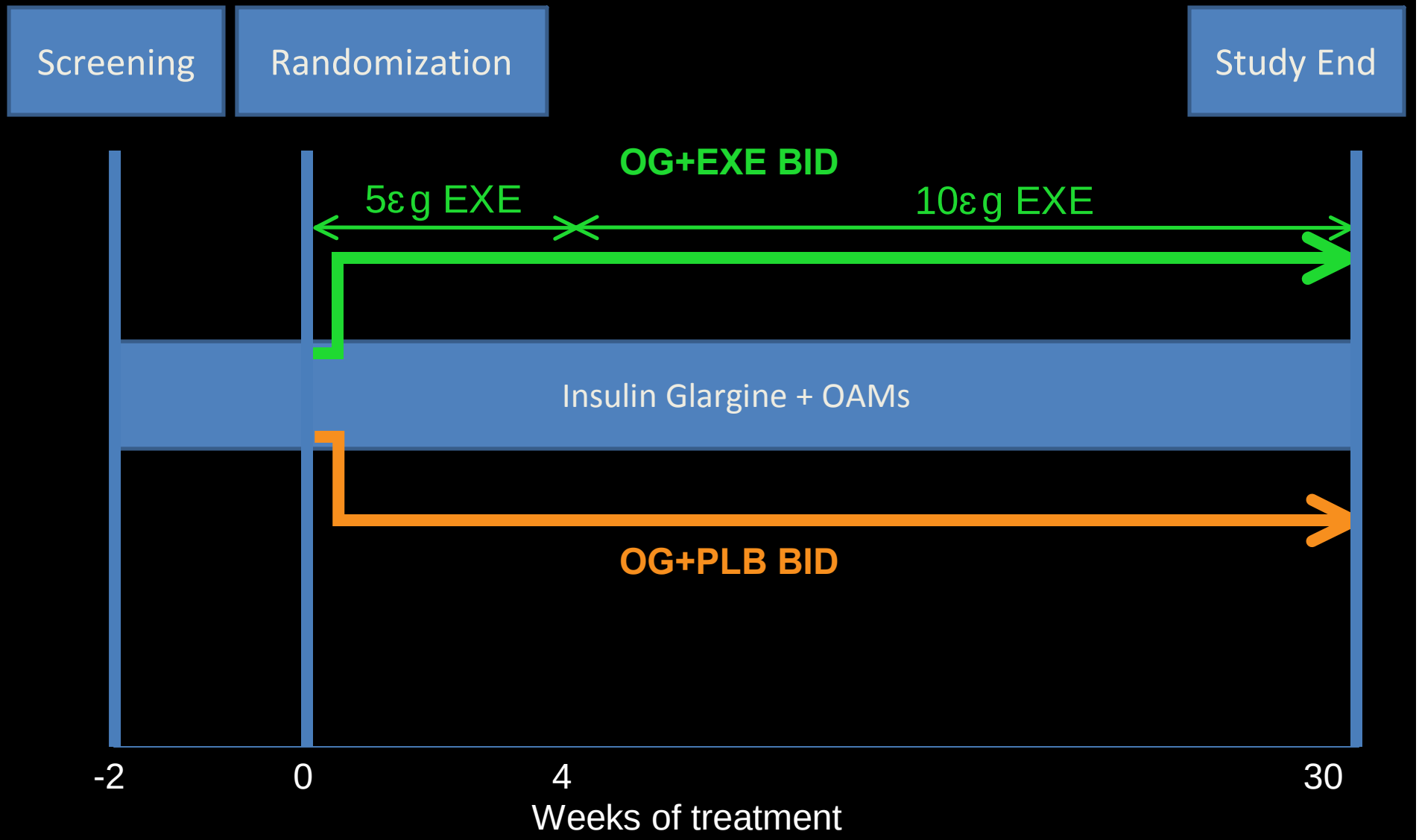

## Evolution of HbA1c in the randomized population (n=343)




HbA1c in all subjects (n=785) = 9.8 at run in and 7.3 at randomization

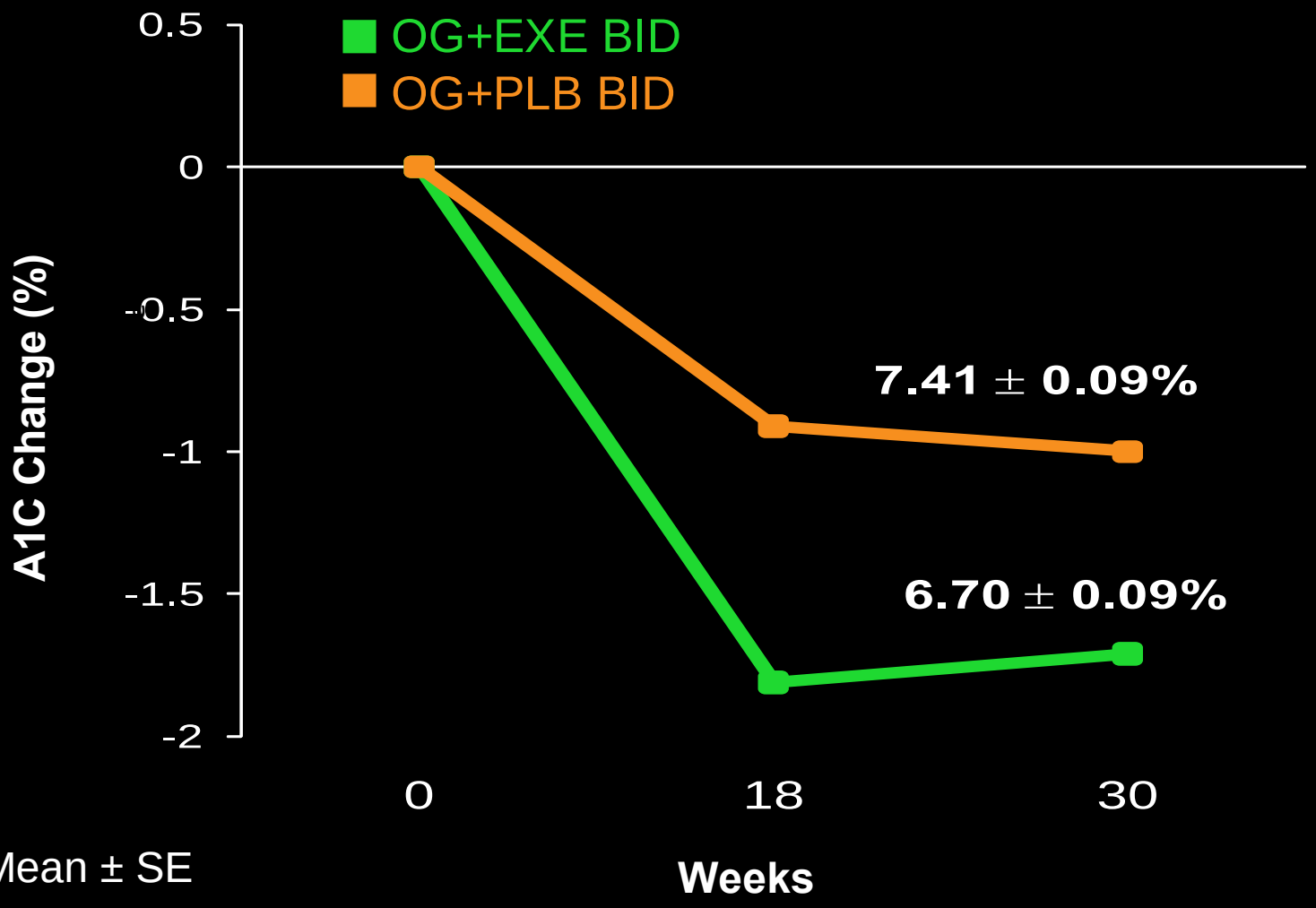
Adapted from Raccah D. http://www.fesemi.org/grupos/obesidad/noticias/ponencias_iv_reunion/Prof.%20Denis%20Raccah.pdf. Accessed April 9, 2010. Cited as sanofi aventis, data on file.

# GWCO - Study Design




Buse, et al. ADA Scientific Sessions Late Breaking Abstracts, #10. June 2010

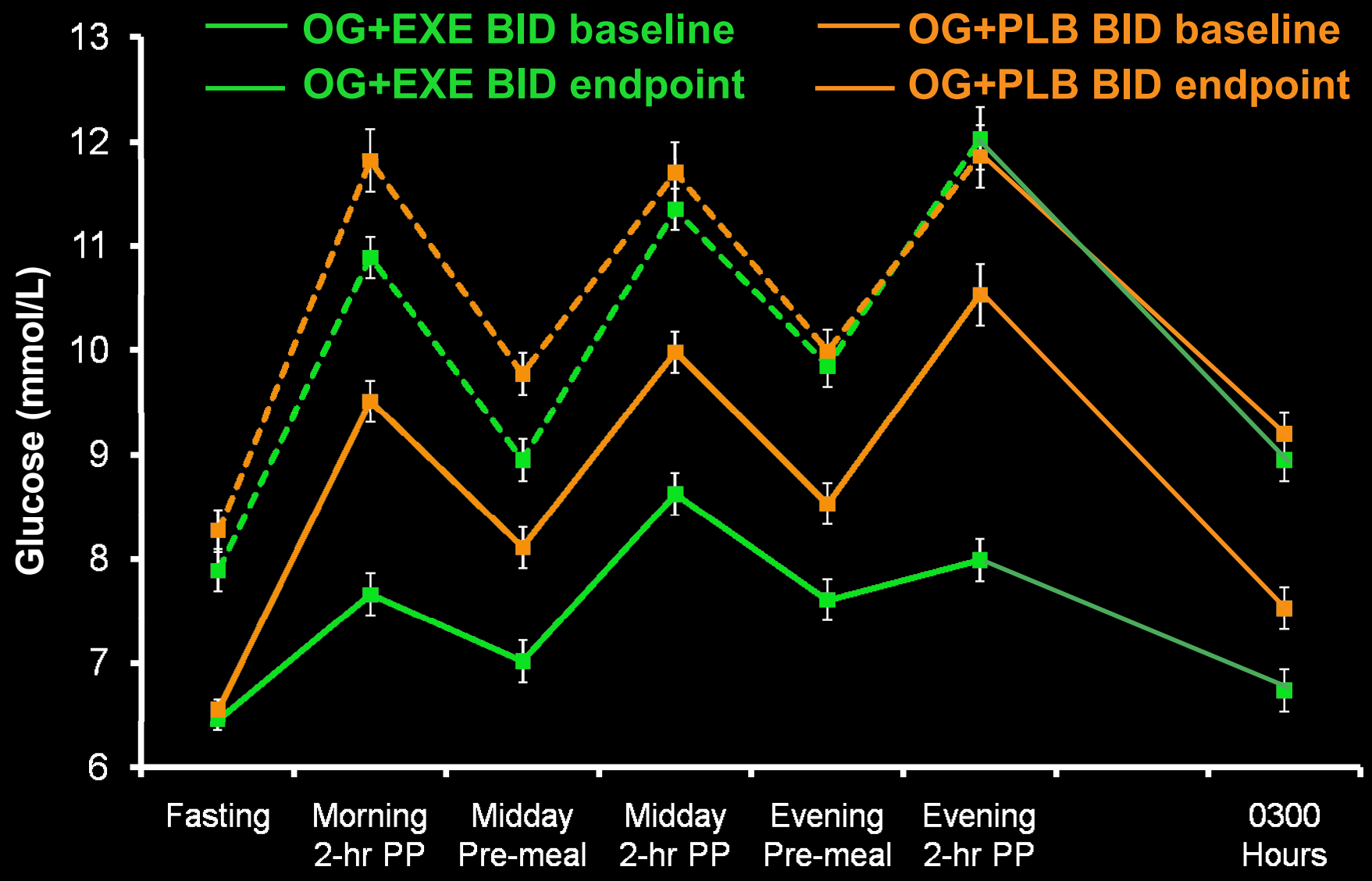
# GWCO: A1C Change from Baseline




LSMean ± SE

Buse, et al. ADA Scientific Sessions Late Breaking Abstracts, #10. June 2010

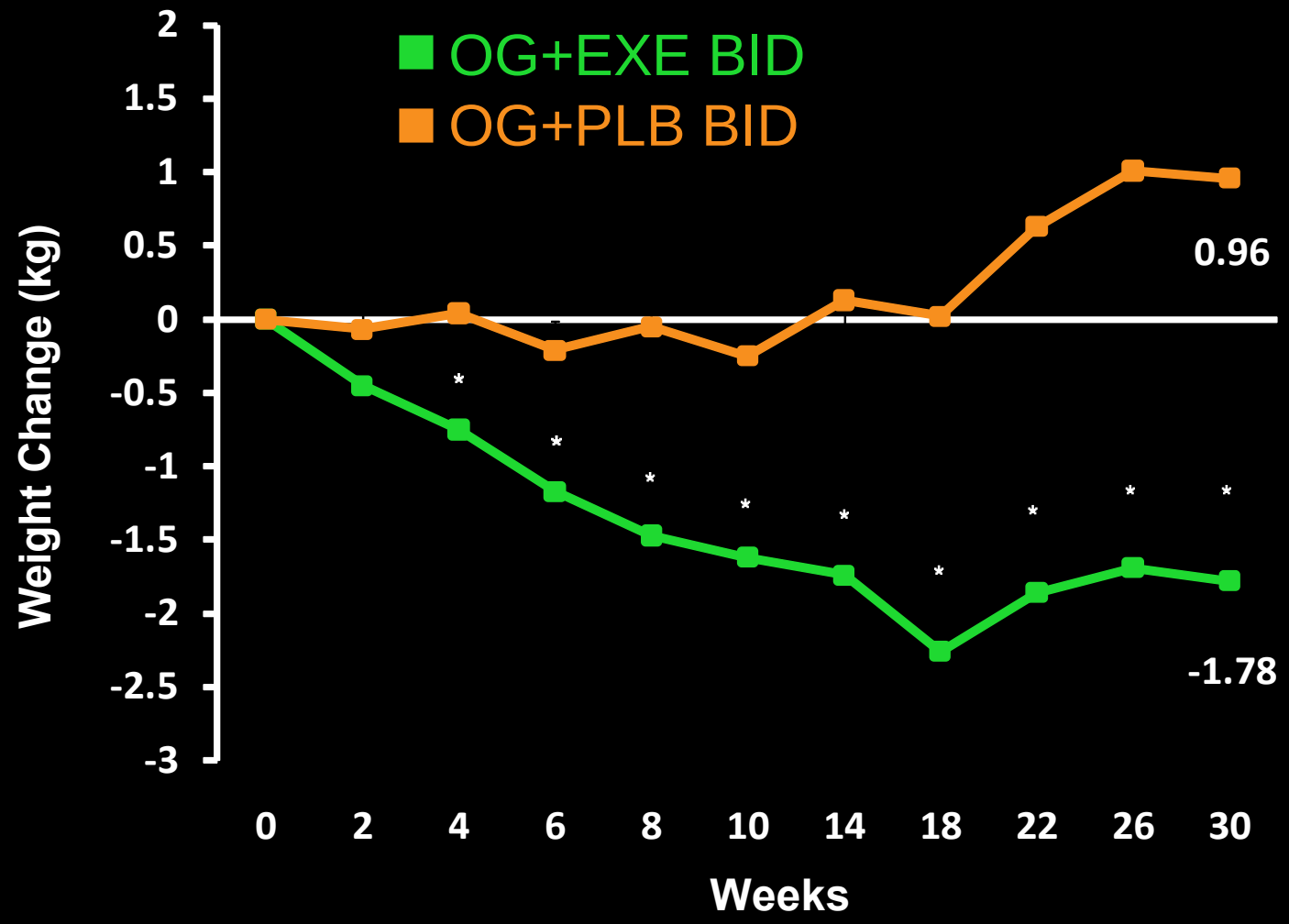
# GWCO: 7-point Glucose Profiles




LSMean ± SE; *p<0.001. Àp<0.01 and **p<0.05 for between-treatment comparison

Buse, et al. ADA Scientific Sessions Late Breaking Abstracts, #10. June 2010

# GWCO: Change in Weight from Baseline




LSMean ± SE; *p<0.001 between-treatment comparison

Buse, et al. ADA Scientific Sessions Late Breaking Abstracts, #10. June 2010

# GWCO: Safety and Adverse Events

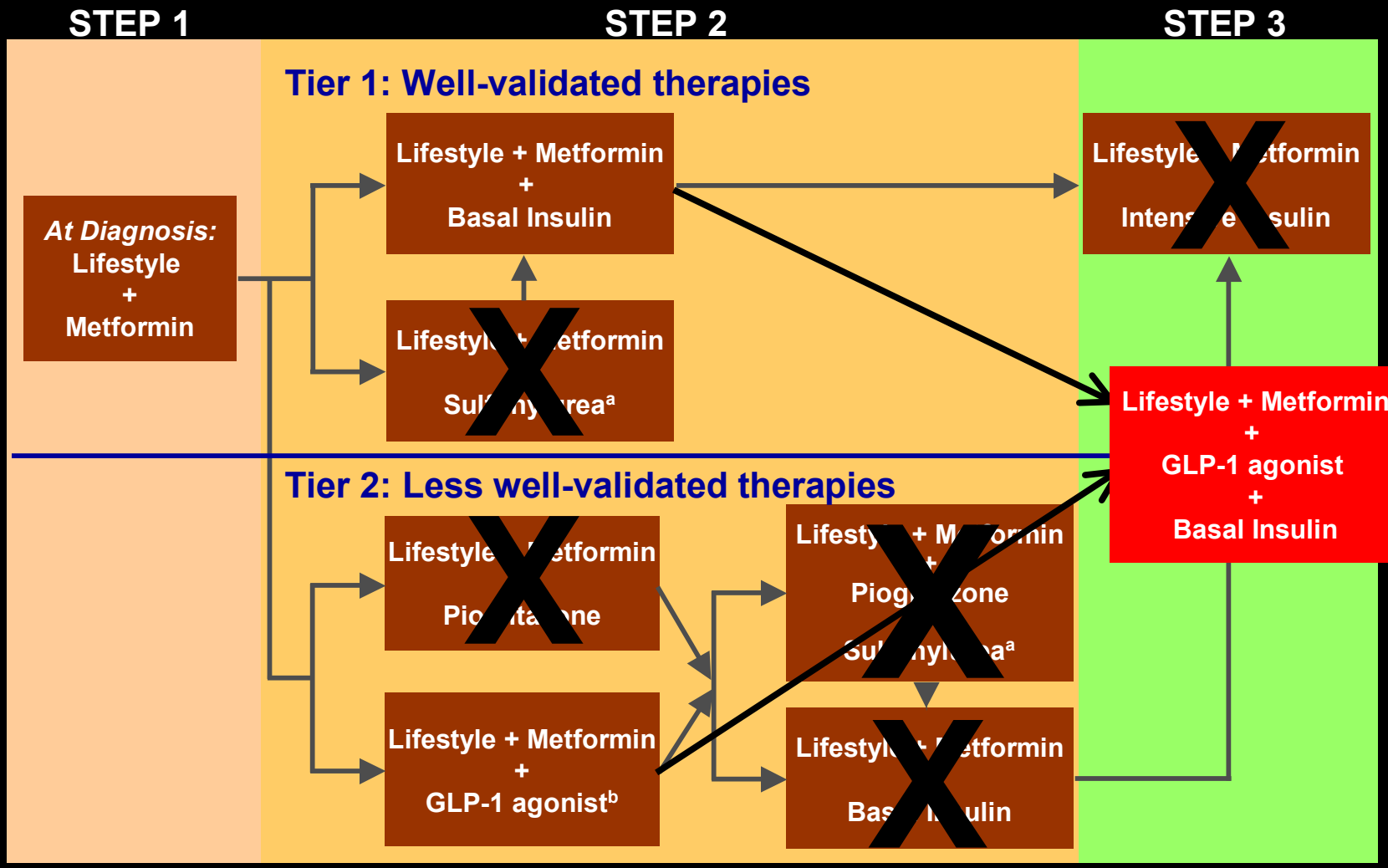
| | EXE BID | PLB BID |
|---|---|---|
| **Minor Hypoglycemia (n [%])** | | |
| Overall incidence* | 34 (25%) | 35 (29%) |
| Rate (episodes/patient/year)* | 1.4 | 1.2 |
| **Adverse Events (n [%])** | | |
| Nausea† | 56 (41%) | 10 (8%) |
| Diarrhea† | 25 (18%) | 10 (8%) |
| Vomiting† | 25 (18%) | 5 (4%) |
| Headache† | 19 (14%) | 5 (4%) |
| Constipation† | 14 (10%) | 2 (2%) |

One placebo patient experienced 2 episodes of major hypoglycemia

*No significant differences between groups; † $p<0.05$, between-group comparison

Buse, et al. ADA Scientific Sessions Late Breaking Abstracts, #10. June 2010

# Updated ADA/EASD Consensus Algorithm




Reinforce lifestyle interventions at every visit and check A1C every 3 months until A1C <7.0%, then at least every 6 months thereafter. Change interventions whenever A1C ≥7.0%.

[a]Sulfonylureas other than glybenclamide (glyburide) or chlorpropamide.

[b]Insufficient clinical use to be confident regarding safety.

Nathan DM, et al. *Diabetes Care.* 2008;31:1-27

- Should we go further in managing diabetes using classical techniques?
  - *Probably not*
- Should we back away from current targets?
  - *No, but we need to individualize treatment.*
- Where are the opportunities?
  - *Screening to detect cases early*
  - *Simplifying therapy*
  - *Adherence*
- Challenges?
  - *Health care reform/economics*

# Diabetes Management: *The Big Picture*

| FOCUS | MEASUREMENT | GOAL | FREQUENCY |
|---|---|---|---|
| GLUCOSE | A1C | Less than 7.0% | Every 3-6 months |
| | Before meal, bedtime, and mid-sleep finger-prick glucose | 70-130 mg/dL | As needed to ensure control and to avoid hypoglyc. |
| | 1-2 hours after meal finger-prick glucose | <180 mg/dL | As needed to ensure control |
| BLOOD PRESSURE | Office blood pressure | <130/80 mm Hg | Every visit |
| CHOLESTEROL | Apolipoprotein B (ApoB-100) | <90 mg/dL (<80 mg/dL with vascular disease, smoking, fam hx early CAD, HTN) | Annually; more often while adjusting treatment |
| | -or- Non-HDL cholesterol (total cholesterol – HDL chol.) | <130 mg/dL (<100 mg/dL with vascular disease, smoking, fam hx early CAD, HTN) | |
| | -or- LDL cholesterol (requires fasting) | <100 mg/dL (<70 mg/dL with vascular disease, smoking, fam hx early CAD, HTN) | |
| | HDL cholesterol | >40 mg/dL (>50 mg/dL for women) | |
| | Triglycerides (requires fasting) | <150 mg/dL | |
| WEIGHT | BMI | 18.5-24.9 kg/m$^2$ (promote weight loss if ≥ 25) | Every visit |
| KIDNEY | Albumin-to-creatinine ratio; creatinine – estimated GFR | <30 mcg/mg; Stable (>60 mL/min/1.73m$^2$) | Annually |
| FEET | Complete exam | Can feel 10 gram filament, vibration testing, normal pulses, skin, structure, gait | Annually |
| EYE | Dilated eye exam | Normal | Annually |
| CVD | History and physical | No symptoms, aspirin if CVD or >40 or multiple risk factors, stress testing with symptoms | Every visit |
| DEPRESSION | Are you sad or blue? | Not usually | Every visit |
| TOBACCO | Medical history | None | Every visit |
| SEX | History | No concerns; contraception | Every visit |
| LIFESTYLE | History | Appropriate nutrition and physical activity | At diagnosis; at least annual update |
| DENTAL | History, exam | Exam (dentist), twice annual cleaning | Annually |
| EDUCATION | History | Understands all aspects of care | At diagnosis; annual update |
| GENERAL HEALTH | History | Vaccines, cancer screening, liver test (ALT), etc | Review at least annually |

Buse JB. Standards of Care. In: The Uncomplicated Guide to Diabetes Complications, 3rd edition. Pfeifer M, ed. American Diabetes Association,.